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Medical Care and Public Health Services

HAVEN EMERSON, M.D., New York

• Medical care applies to the individual, and public health to the community. One is the concentrated application of diagnosis and treatment for the life, the comfort of a patient, and includes guidance in health as for motherhood, infancy, childhood and old age.

Public health services, provided by the community through its local government and the local department of health, are concerned with the prevention of diseases of all kinds. Some are controlled by sanitary authority, but the majority of preventable diseases are dealt with by public health education.

It is not the function of the health department to treat the sick. The family physicians, the hospitals and dispensaries provide for medical care. Medical care of the sick and public health protection are two parallel activities to make use of medical science, one for treatment, the other for prevention of disease.

AS THE SPEAKER at the annual Ether Day celebration at the Massachusetts General Hospital in October 1915, I first ventured to express a point of view upon preventive medicine and its dependence primarily upon personal services of the family physician which you now ask me to develop 37 years later on the other side of our continent which calls the Pacific Ocean its last frontier.

There remain today, I believe, still critical and effective, the same distinctions and definitions to determine the relative functional necessities and usefulness of medical care of patients and the services of the local health department to the community.

What I mean by medical care is that entire range of applied science and the arts of medical practice included in the three words, *diagnosis, treatment* and *prevention* of disease—that is, medical science and art applied to the individual, who is sick, or fears he may be sick or wishes to preserve his health.

I know of no more comprehensive duty or privilege than that of the physician called upon by family or individual to bring relief from the presence or fear of pain, suffering or disability to a person or household that seeks his skill and sympathy and offers every useful aid and collaboration.

This constitutes the substance of medical care. All skills and resources commanded by the physician are focused upon the one and unique person, his patient.

Guest speaker's address: Presented before Second General Meeting at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

In spite of multiple births of identical offspring, we know that Nature never repeats. Biologically and genetically each of us is but one expression of an infinite variety of patterns of body, mind and emotions. Disease and its symptoms are at least equally varied. The aim of the physician is to recognize any deviation from the optimum of structure and function, to understand causes and results of the protean exhibits of disease, anxiety, despair, injuries of the

body and spirit of man, to relieve at least, cure if possible, and as promptly as may be to restore the ailing person to all the satisfactions of life of which he may still be capable, not forgetting to explain what the physician knows and the patient can understand of the preventable factors of his sickness to be avoided in the future.

Less often but fortunately with greatly increasing frequency the physician today is called upon to plan a way of healthy living for babe or mother or grandparent, to apply his knowledge of physiology rather than his pathological acumen. In entire absence of pains or aches in his patient, the doctor lives up to his name as teacher of the laws of right living, to offer a plan of health, to encourage not only the science but a philosophy of preventive medicine among his fellows, and promote a spirit of devotion to the truths of human biology in the hope that much disease will be by-passed and health be more often a continuous and happy experience.

This is medical care, curative and preventive, and personal in its application, whether provided through group or institution or agency, through services of the lone practitioner or by the assembled skills of several. The essence of this is the uniqueness, the personal quality of the need or demand for care and the individual characteristics of the professional attendance concentrated upon the one and only problem of instant importance, the better or continued health of a patient.

This it is that we as the medical profession are in full cry to preserve, to protect, to develop and make so nearly universally available as the servants and the served, time, circumstance, distance, transport and other resources permit. This is the medical care we believe to be best, or perhaps only possible, on the basis of mutually sought and offered services between the licensed practitioner of medicine as a free agent and the parent or child, workman or employer, rich or poor, who is in need of the doctor of his choice.

It seems to me improbable that any substitute for such personal medical care can be developed through the mechanism of civil or military government by the compulsion of laws, or in the presumed interest of economies or uniformity of distribution.

That we have not achieved such a medical service utopia nationwide is well known to all physicians, but we are further on the way than the most optimistic of us hoped a generation ago and there seems no doubt in popular opinion that some pattern can be offered which will hasten the goal and raise our sights to the very best medical care which we see here and there achieved chiefly through the obstetrician, the pediatrician, the internist and the general family physician.

In my opinion it has been in our country through the broadening superiority of medical care that most of the gains in life expectancy, increasing longevity and betterment of survival at every decade of life have been achieved.

Please hold this rather crude and hasty sketch of medical care in mind while we think through the meaning of public health services.

With emphasis on *public* we can best think of those sciences, educational disciplines, authorities under the law and popular informational services which can be made effective only by governmental agencies and voluntary organizations developed and authorized primarily for the prevention of disease and for demographic and social purposes rather than for the benefit of the sick individual.

If we subscribe to the wise and tolerant democracy of Abraham Lincoln, we can well recall his words of nearly a hundred years ago:

"The legitimate object of government is to do for a community of people whatever they need to have done but cannot do at all or cannot do as well for themselves in their separate and individual capacities. In all that the people can do as well for themselves the government ought not to interfere."

Would that some measure of this philosophy prevailed in Washington, D. C., today.

Permit me then to apply this simple and understandable criterion to the problem, the question, the discussion of the necessity for government to undertake the application of the sciences of preventive medicine.

The purpose of a public health service (and we shall for the moment consider only local jurisdictions within the structure of our sovereign states and not the field of national and international health organizations and functions) is to protect a community, a group of people, served by their own elected civil government, against the known preventable diseases, to control environmental factors for the safety and wholesomeness of life, and to provide leadership and authoritative direction in education of the people in any and all matters affecting their health. As Dr. Henry J. Bowditch of Boston wrote in 1876: "The study of the prevention of disease is the only branch of medical learning which the state can legitimately undertake. The practice of medicine and surgery and the appropriate use of drugs must be left to medical schools and to private practitioners of medicine. The state, as a student of the causes of all diseases, only supplements, and indeed nobly supplements, them."

Public health services consist of the application of the sciences of preventive medicine under government or with its approval for social or community ends.

It is such services that have brought benefits of wide variety and deep importance to contemporary society and have made possible the amazing tri-

umphs of productivity, of prosperity, of cultural and economic progress which we see about us. It is by using the resources of the community, of local government, of the authority of statute law and local ordinances to supplement the efforts of private medical practice that the public credit and popular esteem for public health officers and departments has been so commonly earned and well justified.

There is no gratitude comparable to that shown by the mother to her doctor for saving the life of her child. Something akin to this, but less often understood and declared, is the confident trustfulness of a community in the protection against pestilence, against sanitary hazards, and in the utterly unselfish timely warning of any preventable factor of environment, season or circumstance of employment given by the health officer to the people he serves.

BASIC FUNCTIONS OF A HEALTH DEPARTMENT

To a gathering of any physicians and especially to such as have shared in the promotion and development of the kind of local health services that reach 95 per cent and more of the people of California, it should not be necessary to elaborate upon the basic required functions of a local health department. Suffice it to remind you that each of the half dozen principal duties of a local health department has been so long and so widely tested as to usefulness, methods, costs and results that there can be no controversy as to their proper place among the functions of any jurisdiction of local government that presumes to represent universal suffrage and the taxpayers. These basic functions have been included within the scope of local government for a scant hundred years, while the sphere of the physician in medical care has been broadly comprehensive and consistent in its expansion for more than a thousand years.

Briefly let it be said that only those services are usually offered by or required of a local health department which can not be done by physician or patient in their private capacities or by an organized voluntary community resource, or have been assigned to some other more appropriate executive branch of local government. There are many instances where functions other than those essential for public health have been assigned to the local department of health. These may constitute a threat to the administrative integrity of the local health department.

Registration of births, notifiable diseases and deaths; isolation, quarantine, and in certain situations immunizations, and examination to discover unreported or unsuspected cases of communicable disease; public health laboratory services both optional and required, for diagnosis, analyses and epidemiological inquiry; sanitary supervision and enforcement of standards of cleanliness of persons, premises and processes, especially of perishable foods, and of the disposal of human and trade wastes, and the control of animal and insect vermin and pests and of the conditions of employees in industry and commerce—these four functions underly and express all the authoritative or compulsory functions of a local health department.

Two others of a quite different character and free from any taint of obligatory or law enforcing features have been of more recent origin (since 1912) and were at one time attacked by physicians. These are, here and there, still subject to local controversy as possibly an intrusion on the physician's province and an unwarranted invasion of the traditions of private family life and opinions.

Of these two functions of a modern local health department one is intended to bring an understanding and sound practice of maternity, infancy and child hygiene into every home where marriage, the prenatal state of an expectant mother, infancy, the preschool age, the school child through adolescence or into employment presents problems of social significance not commonly brought to the attention otherwise of the family physician. After some forty years of almost universal acceptance by physicians and local communities of the effectiveness and protective value of such maternal and child health services, as they are briefly called, it seems to me we may without cavil accept this educational effort in human biology as filling a permanent place in the public health picture and as basic for any intelligent and constructive plan to better the quality of the following generation and build bodies and minds and emotional maturity to meet the problems, the wear and tear, the trials, hopes and frustrations of the adult state.

The most lately developed of the building-stones of a sturdy structure of public health service is that of health education, the only other resource of a government agency to influence the people's manner of living besides the use of authority. The persuasive influence of teaching the truths of personal hygiene, both physical and mental, constantly increases while the police power, the strong-arm methods of sanitary ordinance and public health laws, is less and less resorted to.

These six functions of local health departments, four effective because of the weight of compulsion or force of law and two based on the enduring value of education in the principles of human biology, constitute the hard permanent core of a program for nationwide health without each of which no community can reap the best results of progress in the sciences of preventive medicine. These public serv-

ices supplement and reenforce the influence and advice of the family physician and his specialist colleagues in the case of the individual sick patient or healthy person seeking guidance.

From this point onward and beyond into a broadening field of new projects of public concern, bordering on both medical care and public health, there are matters of principle and practice, fact and opinion to be considered.

If I am not mistaken, final and sound decisions in respect to some of these more recent interests will depend upon the definitions we agree upon and the differences of emphasis we give to at least three principal factors, namely individual versus collective facilities for medical care, education of both physicians and the community at large in the truths of human biology, and the assignment to the local health department of new duties perhaps equally or more appropriate for other departments of government.

At least the following fourteen objects of current public solicitude and professional concern are now either well established in the pattern of local health department functions or are being urged upon the health officer by influential and persuasive groups in his community that have very considerable funds to spend and have wide publicity and lay opinion to promote them.

1. Chronic sickness and disability in young and old.
2. Aging, its prevention and protection.
3. Rehabilitation of the physically and mentally handicapped.
4. Treatment of crippled and disabled children.
5. Rheumatic fever, prevention and management.
6. Cerebral palsy, prevention and reconditioning.
7. Multiple sclerosis, prevention and care.
8. Cancer, prevention, diagnosis, treatment.
9. Heart and circulatory diseases, prevention and care.
10. Mental health, guidance and protection.
11. Diabetes, detection and guidance.
12. Alcoholism, management of addicts.
13. Narcotic addiction, registration and control.
14. Infantile paralysis, treatment and rehabilitation.

Good administrative practice would seem to favor the concentration of all educational endeavors, which contribute to prevention and are not provided for the people in established educational institutions such as schools, colleges and universities, under the local department of health; institutional and custodial care of the sick and relief of indigency, dependency and delinquency under such agency as is already familiar with these necessary social duties, but certainly not the department of health; diagnosis and treatment of all variety of sick persons, other than those suffering from communicable or mental diseases, to be a function of medical practitioners or groups of them serving as at present in all variety of illness in their offices in general hospitals and in dispensaries. There is sound specialization in administrative medicine as in clinical medicine.

It is obviously of the first importance that any disease or group of aging, sick or disabled persons of sufficient number and condition to rouse public sympathy and active efforts is a proper subject for study, statistical, epidemiological, demographic and economic by the Department of Health of local, state or national government, to discover what if any are the preventable factors and how the knowledge of them may be put to work to reduce prevalence or disabling results or death from such diseases. Such studies do not require that the patients themselves be cared for by each local or state department of health, but can perhaps be best carried on by such institutions as are to be found in the National Institutes of Health. If we do not require constant concern with prevention by the Department of Health, we shall find the insistent demands of the sick diverting the slender professional resources of this department into directions for which health officers and their staffs were not trained and for which other physicians, nurses and medical institutions are much better qualified.

The care of the chronic sick and disabled, and of the aged, the rehabilitation of amputees and hemiplegics, the training of industrially crippled for reemployment, management of chronic heart and arterial disease, radiation and surgical therapy of cancer, orthopedic and other care of crippled, disabled, rheumatic and cardiac children, the alcoholic, the diabetic, the postpoliomyelitic paralytic, the cerebral palsy and multiple sclerosis patients all require the skills of the appropriate clinician and the assembled facilities of the general hospital, of the local community, region, base or university medical school areas as do other categories of the sick. The community hospital, *general* in fact as well as in name, is more appropriate as the agency for medical care than is the local health department.

It is for the health department to study the phenomena, the natural history of disease as it is expressed in groups of people because of some common factor possibly preventable. Then when anything is learned likely to be of value, the story should be told to the doctors and patients, the ways of prevention if any should be demonstrated or provided and the people be persuaded to make suitable provision for the care of those sick who need treatment in their homes or in appropriate institutions. The health department can well be, and generally is, the

guiding community influence and can show the need and possibilities of remedy of preventable factors of disease and injuries without itself being charged with the operation of hospitals and dispensaries or with the care of the sick individual.

The field forces of the department of health are likely to be able to discover by routine visits to families and households, shops, schools and other occupied premises unsuspected cases of the disease under inquiry, whether of cancer, mental or occupational disease, diabetes or other disability. The organization of office and field personnel and equipment is certain to be needed and to be the major factor in systematic search for diseases of insidious development such as diabetes, cancer, and heart disease wherever the state of public opinion and medical cooperation make mass surveys acceptable and welcome. Few social and medical techniques have been so productive of knowledge of the amount, character and location of certain categories of diseases of nutrition, tumors, heart disease, tuberculosis and syphilis as have the systematic community and regional surveys made cooperatively by the medical profession and the health department.

SCREENING TESTS

The effort to screen a large part of the community by several routine production-line diagnostic or descriptive tests is but a passing phase of technological gadgeteering which leaves the patient uninformed and the physician to whom the report of findings is sent, forced to repeat most of the work with a history sheet in hand. As Dr. Wilson G. Smiley[5] so clearly stated in his address before the Southern Tuberculosis Association, September 10, 1951, "Multiple screening is inferior medicine, poor, slipshod, shortcut medicine and furthermore poor public health." However, there may be some promotional value in the so-called "multiphase screening" which will persuade many people to seek a really adequate health examination from their own physician who knows their performance in sickness and health and can give due consideration to the significance of minor deviations from normal.

It is well for physicians with a family practice to remember that the process of preventing large numbers of illnesses that used to call for much medical service has in all instances resulted in an increase in medical demand in other directions. The survival of a multitude of infants, young children and youth from the acute infections has at least trebled the proportion of people over 65 who need medical assistance throughout the lengthening years.

As I see it there is nothing in the prospect of local health services at all likely to reduce the demand for competent practitioners of medicine in increasing numbers everywhere except perhaps in the already oversupplied cities of the country. Every advance in preventive medicine adds to the opportunity of medical care by the family physician and ties the health department more closely to the ambitions of the community for social progress.

The deciding voice that will determine the future direction and character of medical care undertakings and public health services will be that of the consuming public, the people who demand the product which medical education and license to practice have entrusted to us as physicians.

The same consuming public through its elected officers of local government, city or county, agricultural or industrial will decide what services it will demand from and assign to the health officer and his organized team of associates, engineer, nurse, educator, dentist, veterinarian, laboratory and statistical technicians.

It is quite beyond all reason and more than improbable that any state legislature or the Congress will seriously consider legislation which would hamper local government in the free exercise of its established right to demand and support public health services of a nature and extent to satisfy its particular ambitions for protection against the hazards of preventable disease and the vicissitudes of illness for which we have neither preventive nor curative measures. No minority of citizens, medically educated or other, can prevent local government from determining its public functions.

We in this country have chosen a way of life of infinite variety and left the choice to the voice of the majority. It is quite distinctly the responsibility of the medical and associated professions to make clear to the public the scientific basis for the care of the sick and for health protective services. There is no greater danger facing our nation than a confusion and controversy of facts and opinions as to the best way to invest shrewdly and reap increasing dividends from the stock of knowledge accumulated by the sciences of preventive medicine and waiting to be implemented through the resources of individuals and society as a body. The progress of science will set at naught any plans or pressure for legislative limitation of the scope and functions of public preventive medicine.

There are a few and well tested social devices to bring common understanding as to the application of medical care and public health services, the methods, costs and results. It is time that we applied these to this unfinished business. The elements appear to me to be of three kinds, local government with its executive department of public health, community health councils representative of educated public opinion, and the local medical society with its membership organized to study local medical needs and

resources for care of the sick and for public health. Comparable elements are desirable on a state basis.

Until there is substantial organization of public health departments at the local and state levels of government and a good variety of experiment and experience among them, the vague and mostly political platitudes offered as "national health plans" either by federal government spokesmen or by nationwide professional bodies are of no serious import and lack reality or competence. We have today no national plan for medical care or public health services worthy of the name, and are not likely to have any until we have applied ourselves successfully to the solution of some of the simpler problems of the home-town, the county, the state district, trade area or transportation centers of our country.

Instead of the potentially 150,000 local health jurisdictions in the 48 states, we need about 1,500 as the maximum. We have now about 1,200 authorized and mostly organized under full time trained medical officers of health. In six states all the population and area is included within such local health units. In ten more states 90 per cent or more of the population is so served; in seven additional states between 75 and 90 per cent of the population is served. And yet some 27 per cent of our people (approximately 40,000,000) live in communities lacking full time professionally qualified health direction and most of the basic health services. For less than 5 per cent of the people of the United States does the staff of the local health department meet the minimum desirable ratio of doctors, nurses and sanitarians in proportion to the population for good local health service.

There is a state health department in each state, in all but two instances committed to the policy of local health jurisdictions as the basis of total nationwide coverage.

In 33 states and 1,100 local jurisdictions there are representative health councils.

In all states and in most of the 3,070 counties there is an organized body of physicians.

If it were not for the duplicating and competitive construction of Veterans Administration hospitals and the reduction in the amount of federal grants to help the less favored local communities of our states to complete their respective programs of hospital building, we should now be almost abreast of the civilian need for general hospital beds. We need many more beds for the humane and competent care of the mentally ill. The margin between estimated desirable number of beds for tuberculous patients and those actually available grows steadily less and in another ten years we may well find that reduction in cases of this disease and improved methods of treatment in and out of hospitals, with shorter periods of necessary separation of such patients from their families, may at last close the gap and permit some diversion of beds in these hospitals to patients in other categories of long time illness such as arthritic, neurological and cardiac disease.

PERSONNEL SHORTAGES

Increase of the ratio of physicians to population is assured by the acceptance and graduation of more medical students than has been practicable before. If we are spared the calamity of war and the continued drain of physicians from civil life to meet the needs of the military establishment and for loan to countries and peoples far and wide around the globe who still lack the knowledge and skills our physicians are able to take to them, we shall in the foreseeable future be able to provide for what may be called the normal demands for personal and institutional medical care of an increasingly competent quality.

The most serious threat to good medical care particularly in hospitals is the continuing and distressing shortage of registered nurses. Remedies for this situation are being sought through changes of educational policies and replacement of the registered trained nurse in many hospital positions by the less well prepared practical nurse and nurse attendant, but an easy and early solution is not yet assured.

The picture of public health services is much less favorable because of the even greater shortage of physicians, nurses, sanitarians and health educators, the major factors being the demand for such trained personnel by the federal government, voluntary health agencies and industry, and the lower salary scale offered by local and state governments that find it difficult to recruit and hold physicians and nurses in civil service employment or subject to merit system qualifications in competition with the much higher earnings possible in the clinical branches of medicine and in federal service.

It is probable that all but the most sparsely settled and impoverished areas of our states would soon, within five years, be organized and operating their local health units if they could obtain the medical, nursing and other professional personnel necessary to do a good job of public health service. Inflation and the national defense preparedness effort have caused serious delays in the attempts of the past ten years to achieve total coverage of our population and area with adequately staffed, directed and financed local health departments.

The demands by organized society and local governments for the benefits of modern medical science cannot be denied. Whether we as physicians or patients wish it or not, we are inextricably involved in a revolution of human values in which the importance of the individual, the family, the social outlook

of the community have assumed colossal proportions. The general public has been heavily oversold by many voluntary agencies with a disease hobby.

They want medical care for the sick, early, prompt, skilled, sympathetic and at a cost within collective resources through prepayment plans if not always by the individual patient's means at the time of the physician's service. The public wants its local government and its voluntary social resources welded into an instrument for the prevention of disease, the protection and promotion of health.

Our role as physicians is to know the needs and possibilities of service to the sick and the healthy as well as to recognize the quality of social pressures, sometimes misdirected and misled. We must be aware that we know more than we put to work of the causes and prevention of diseases, and we dare not underestimate the danger that the people in their haste and ignorance may take the management of medicine into their own hands to our profession's ultimate confusion, and to the public's loss.

As the hospitals and their outpatient departments and organized professional staffs and the office and home visits of physicians serve the sick and carry on a continuous process of *personal* preventive medicine, so the health department and its team of associated professions under medical leadership deal with preventable diseases *wholesale* and protect the mass of the community against hazards of personal contact, of environment, inheritance, occupation and the accidents of a complicated and strenuous life. The hospital and the health department are twin symbols of the community's concern with the application of the sciences of medicine to the comfort and safeguarding of the people, whose health is the only permanent wealth of nations.

Medical care, as I understand it, is the chief purpose of the physician sought by the sick and by the well for personal individual benefit. At best, it is a long continuing relationship through many years of observation with consecutive record of experience of the episodes of illness and of performance of the body, mind and emotions in health. Medical care calls for a variety of cooperative professional skills, for diagnosis, treatment and prevention of disease. Institutions and agencies devoted to medical care have grown great and given incalculable benefit to generations across our land without any dependence upon or administrative relationship with local health departments. Social evolution and demand may alter this pattern of medical care, but any radical change from the tested and trusted personal and direct responsibility between patient and physician, which has been productive of much of our national good fortune, should be subjected to competent examination before adoption.

Public health services to be effective do not need to include care of general sickness. Prevention of disease at wholesale through civil government by education and sanitary authority is the special distinctive function of local and state health departments. Only where the resources of the community must be enlisted to make preventive measures effective should a new public health function be added to the basic services everywhere recognized as necessary. Without the local health department, the structure of state and nationwide public health administration is likely to be wasteful and ineffective. Not primarily the *person* but the *community* benefits from local health services which will always be best when supplementing, not replacing or competing with the private physician.

There need be no rivalry between the medical profession and officers of public health except in the process of doing their respective jobs in the closest cooperation. Neither legislatures nor the courts will hinder the freedom of the physician to expand his conquest of sickness nor limit health departments in extending their duties to new realms of preventive and constructive public health if each of these partners in the sciences of medicine respects the other's superiority and special competence and the two together devote themselves without stint to the public interest.

156 East 79th Street.

Cardiorespiratory Function

HURLEY L. MOTLEY, M.D., *Philadelphia*

• Accurate evaluation of the degree of impairment of pulmonary function in persons with fibrosis and emphysema requires: (1) ventilatory measurements from rapid spirogram tracings (vital capacity, maximal breathing capacity and the time required to blow the air from the lungs); (2) determination of the degree of bronchospasm present; (3) determination of the degree of pulmonary emphysema (residual air expressed quantitatively as percent of total lung volume); (4) determination of the arterial blood oxygen saturation at rest and immediately after step-up exercise; (5) measurement of the oxygen extraction from inspired air (per cent of oxygen removed) during rest and exercise; (6) determination of the oxygen up-take during exercise; and (7) observation of the duration of dyspnea after step-up exercise.

No single physiologic test is adequate in evaluating impairment of pulmonary function, and roentgenograms of the chest are unreliable as a sole basis for appraisal of disability.

In industrial medicine, pulmonary function studies make possible (a) more accurate diagnosis and evaluation of pulmonary disability; and (b) earlier detection and thus prevention of prolonged exposure by susceptible individuals to environmental hazards.

PULMONARY FUNCTION has been evaluated on a basis of the ability of the lungs to supply oxygen to and remove carbon dioxide from the blood during rest and exercise. In the large majority of cases of pulmonary disease with dyspnea the disability has been found due to fibrosis and emphysema. So great is the pulmonary reserve in man that clinical or roentgenologic detection of those conditions at an early stage is difficult. Physiologic tests of pulmonary function in addition to the clinical and roentgenological examination have been found necessary to appraise lung function accurately in the presence of fibrosis and emphysema. Physiological tests have been studied and analyzed with respect to the early detection of susceptible individuals to environmental hazards before serious stages of disability develop, for the early recognition and removal of such persons would greatly benefit both employees and industry.

The basic data for this discussion were obtained from a study of 500 miners of soft and hard coal who had fibrosis and emphysema and respiratory complaints. Physiological studies on such a large homogeneous group supply data from which a satisfactory evaluation can be made of the significance and limitations of the various physiological tests employed in pulmonary function measurements in man.

The measurements made were: Maximal breathing capacity[5] and vital capacity from spirogram tracings employing special apparatus (before and after treatment with a bronchodilator drug); residual air volume by the oxygen open circuit method;[1] arterial blood oxygen saturation both at rest and immediately after step-up exercise by the Van Slyke content and capacity method;[21] direct arterial pO_2 and pCO_2 determinations, by the Riley bubble method;[17] arterial pH at rest and after exercise; oxygen uptake and carbon dioxide output during rest and exercise from direct gas analysis of inspired and expired air;[6] per cent of oxygen extraction by the lungs from inspired air both during rest and exercise; and the duration of dyspnea after one minute of step-up exercise (30 steps on a stool 20 cm. high, in one minute).

Professor of Medicine and Director of the Cardiorespiratory Laboratory of the University of Southern California, and the Hospital of the Good Samaritan, Los Angeles; formerly Associate Professor of Medicine, Jefferson Medical College, and Director of the Cardiorespiratory Laboratory, Barton Memorial Division of Jefferson Hospital, Philadelphia.

Presented at the California Trudeau Society and the California Tuberculosis and Health Association, San Francisco, April 4, 1952.

Spirogram tracings of vital capacity and maximal breathing capacity, residual air volume measurements and exercise tolerance tests are the most important standardized tests of pulmonary function for clinical detection of fibrosis and emphysema. Bronchospasm plays a prominent role in chronic pulmonary disease and this aspect needs to be determined. Determination of arterial blood oxygen saturations and the percentage of oxygen extracted from the air breathed are frequently necessary for accurate evaluation. A mild exercise test is necessary, but not one designed as a measure of physical fitness. Spirogram tracings of ventilation measurements, which are easy to obtain with suitable apparatus, are most useful in screening tests, for abnormalities may be detected by this means long before roentgenologic changes appear.

On a basis of the physiological studies the 500 coal miners were classified into four groups as re-

gards degree of impairment of pulmonary function —slight, moderate, advanced and far advanced.

A complete history, physical examination and radiological study supply important information for the clinical evaluation of impairment. However, such information frequently proves inadequate for an accurate determination of the extent of disability present and in some cases even fails to indicate the nature of the respiratory difficulty. In recent years the discrepancy between roentgenological studies and pulmonary function studies, in the appraisal of disability produced by silicosis in coal miners, has become well recognized in many parts of the world.[2, 3, 7, 8]

In the subjects of this study there was no apparent correlation between the roentgenographic stage of silicosis and the degree of impairment of pulmonary function (Table 1). Third stage silicosis existed in cases in which there was a slight degree of pulmonary function impairment, and advanced degrees of function impairment occurred in cases in which silicosis was only borderline or in the first stage. A lack of correlation of the roentgenographic stage of silicosis and the degree of pulmonary emphysema has been found in both hard[7] and soft[8] coal miners. Roentgenograms of the chest, although useful in diagnosing silicosis, should not be used as the only criteria in disability evaluation. The disease cannot be diagnosed on the basis of pulmonary function measurements alone, but the information available from these studies provides for more exact appraisal of the disability present than is possible by the usual clinical diagnostic procedures.

Pulmonary emphysema and chronic bronchitis are commonly regarded as the two factors producing disability in coal miner's silicosis. The presence and extent of pulmonary emphysema was accurately determined (duplicate checks of 100 cc. or less in all cases) in this study by measuring the residual air volume, using an improved oxygen open circuit method[1, 6] with a demand valve. The residual air volume was expressed as a percentage of the total lung volume (residual air plus vital capacity). This value expresses as a physiological relationship the effect of an increased volume of residual air on the mixing and dilution factor with respect to vital capacity and total lung volume. Thus it is immaterial whether the total lung volume is increased, decreased or remains unchanged, for the percentage value obtained represents the functional value of the pulmonary emphysema. The air remaining in the lungs after a forced expiration is termed residual air, and this normally occupies about 25 per cent of total lung volume.

The 500 cases in this study were classified according to the degree of pulmonary emphysema based

TABLE 1.—*Degree of Impairment of Pulmonary Function as Compared with Stage of Silicosis (Roentgenographically Determined) in 500 Coal Miners with Respiratory Complaints*

Degree of Impairment of Pulmonary Function	Group	Cases Studied		Roentgenologic Classification*									
				Normal		Borderline		First		Second		Third	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Slight	1	82	16.4	1	1.23	10	12.20	15	18.29	27	32.92	29	35.36
Moderate	2	169	33.8	7	4.14	15	8.88	23	13.61	35	20.71	89	52.66
Advanced	3	170	34.0	3	1.77	10	5.88	20	11.76	23	13.53	114	67.06
Far advanced	4	79	15.8	0	0.00	2	2.53	13	16.46	17	21.52	47	59.49
Total		500	100.0	11	2.20	37	7.40	71	14.20	102	20.40	279	55.80

* *Borderline*, increased peribronchial markings; *first stage*, slight fine mottling in parenchyma and increased size and density of hilar lymph nodes; *second stage*, typical nodular round and oblong shadows of soft even density from 2 to 6 mm. in diameter; *third stage*, shadows larger than 6 mm. in diameter and coalescence into aggregates.

TABLE 2.—*Degree of Pulmonary Emphysema (Data based on the residual air percentage of total lung volume in 500 coal miners with respiratory complaints)*

Degree of Emphysema	Classification by Groups	Residual Percentage of Total Lung Volume	Significant Clinically	Cases Studied		Roentgenologic Classification*									
						Normal		Borderline		First		Second		Third	
				No.	Pct.*	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
None	1	25 or less	No	38	7.6	1	9.09	6	16.22	3	4.23	13	12.75	15	5.38
Slight	2	25-35	No†	138	27.6	3	27.27	8	21.62	18	25.35	34	33.33	75	26.88
Moderate	3	35-45	Yes	165	33.0	6	54.55	13	35.13	17	23.94	23	22.55	106	37.99
Advanced	4	45-55	Yes	106	21.2	1	9.09	7	18.92	19	26.76	19	18.62	60	21.51
Far advanced	5	Above 55	Yes	53	10.6	0	0.00	3	8.11	14	19.72	13	12.75	23	8.24
Total				500	100.0	11	.....	37	.....	71	.....	102	.....	279	.....

* See footnote, Table 1.

† If other function measurements are normal, hyperventilation compensates for the slight increase in the residual air volume.

on the residual air percentage of total lung volume (Table 2). Although this percentage grouping is somewhat arbitrary, other related physiologic measurements substantiate the validity of the classification for diagnosis, study and evaluation.[6] Thus in 35 per cent of the 500 cases, pulmonary emphysema was not a significant factor in producing disability (Table 2). Residual air measurements were not obtained during periods of upper respiratory infections or asthmatic attacks or other temporary abnormalities which were clinically apparent, so that the residual air measurement represents the best baseline measurement obtainable in each case. In a comparison study of the residual air volumes at rest and during a steady state of moderate treadmill exercise, in 51 cases the changes in residual air percentage of total lung volume were found to be small (average increase 1.4 per cent) even in extensive pulmonary emphysema.[9] Upper respiratory infections or asthmatic attacks produce temporary decreases in vital capacity and increases in residual air, so that during the involved period, the mixing and dilution problem is increased in some cases to pronounced degree. An increased residual air volume represents a potential hazard which may produce complete incapacity during periods of respiratory infections. A residual air volume over 35 per cent of total lung volume is abnormal and indicates the presence of emphysema in clinically significant degree. In some cases a marked degree of reversible bronchospasm exists. In this condition treatment with bronchodilator drugs results in some reduction of residual air and some increase of vital capacity, but the normal state is not restored and the change in residual air percentage of total lung volume is usually small if the baseline study is obtained as described.

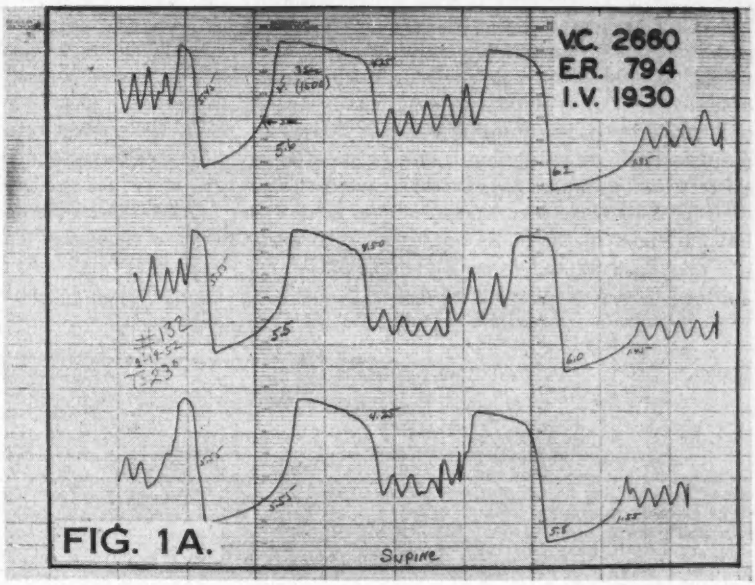
A high degree of reversible bronchospasm may exist without an increased volume of residual air. Some patients with a considerable increase in residual air volume have minimal disability, as compensatory hyperventilation is good, and the dyspnea level is not reached even with moderate exercise. This indicates the value of good ventilation (vital capacity and maximal breathing capacity) in limiting the disability resulting from pulmonary emphysema. A correlation was noted between the degree of emphysema and the incidence of strain upon the right side of the heart,[4] but the typical electrocardiographic findings are absent in about 40 per cent of the cases with a far advanced degree of emphysema (over 55 per cent of total lung volume residual air). Emphysema of a far advanced degree is disabling and the evaluation of disability may be made on this measurement alone. The residual air volume determination is one of the most important function measurements in disability appraisal. An increased residual air volume (above 35 per cent of total lung volume) is abnormal and represents emphysema, not a temporary insufflation of the lungs.

Vital capacity, although a useful and essential measurement, has but limited value alone. In general, vital capacity decreases as the degree of pulmonary emphysema increases[10] but because of the wide range of individual variations the usefulness of this measurement is limited, unless the values are extremely low (less than 1,800 cc. in men) or very high (above 4,200 cc. in men). A vital capacity of 2,000 to 3,000 cc. may exist without emphysema or with a far advanced degree of emphysema, with slight disability or total disability. The shape of the spirogram tracing[7] supplies useful information on the state of the lungs, as well as giving the vital capacity volume. When more than three seconds is required to blow most of the air out of the lungs after a deep inspiration, impairment is indicated. This may be due to loss of elasticity or to obstruction or to both. The time element and the shape of the spirogram tracing should be taken into consideration in analyzing vital capacity tracings (Figure 1). This time factor is usually ignored. The three-second vital capacity represents the maximal portion that is of use, for if a longer time interval is required, the individual cannot make use of the added portion with breathing rates of 12 to 15 per minute.

Maximal breathing capacity is both a time and volume measurement, and the normal values for men range from 120 to 180 liters per minute, depending on the age and size of the subjects and the technique used.[5] In general, if the maximal breathing capacity (MBC) measurement is less than 40 liters per minute in men the degree of pulmonary emphysema and function impairment is significant, but insignificant if the MBC is over 120 liters per minute, and otherwise indeterminate for values between 40 and 120 liters per minute. If the MBC is good, hyperventilation can compensate partially or completely for the mixing and dilution factor imposed by the increased residual air volume in pulmonary emphysema. In general, compensatory hyperventilation is adequate in the absence of other complicating factors for increases in residual air volumes up to about 35 per cent of total lung volume[11] as shown by changes (see Figure 2) in arterial pCO_2 (increased above 40 mm. of mercury). Above this value, however, hyperventilation is often inadequate to maintain normal gas exchange.

Since measurement of the maximal breathing capacity appears to have practical value in the early detection of fibrosis and bronchial obstruction it would seem desirable to take MBC measurements routinely along with chest roentgenograms of industrial workers exposed to dust hazards. If the MBC

Figure 1-A.—Spirogram tracings of vital capacity. Read from right to left. Time intervals between vertical lines, 12 seconds. Vital capacity (VC) was measured both by having the subject take the deepest possible breath after a forced expiration and exhale as far as possible after taking the deepest possible breath. In chronic pulmonary disease one may give a slightly higher figure than the other, but in normal persons there is no significant difference. Note the abnormal shape of the spirogram tracing and the prolonged time required for exhalation after a deep inspiration. The normal exhalation time should be three seconds or less. The expiratory reserve (ER) is the part below the quiet breathing baseline, and the inspiratory volume (IV) is the part above this baseline. The volume of air exhaled in the first three seconds represents the maximal usable part of the VC measurement. The rest of the volume of air shown is nonfunctional.



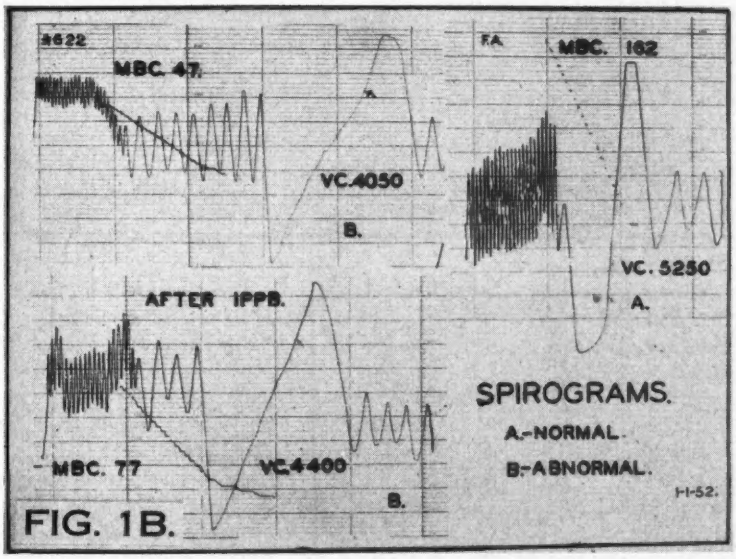


Figure 1-B.—Normal and abnormal spirogram tracings of vital capacity and maximal breathing capacity are shown. Note in the abnormal tracing 22 seconds was required to complete exhalation and although the total vital capacity volume was 4,050 cc., actually the maximal usable part of vital capacity was 852 cc. (that volume exhaled during the first three seconds). The lower part of the abnormal tracing was after intermittent positive pressure breathing (PPB) treatment with a bronchodilator drug, Vaponefrin.® Note the abnormal shape of the spirogram tracing is still present although the maximal breathing capacity (MBC) was increased from 47 to 77 liters per minute.

measurements decrease progressively from year to year, the indication is that fibrosis and loss of lung elasticity with obstruction are developing and the individual should be removed from dust hazards, regardless of roentgenologic appearance of the chest at the time.

The arterial blood oxygen saturation was determined routinely in all cases both at rest (basal type) and immediately after step-up exercise, and in addition in 122 cases during a steady state of treadmill exercise. A comparison of the arterial blood oxygen saturation after exercise with the saturation when the subject is at rest is most important in disability evaluation. If the saturation drops 5 per cent or more with exercise the prognosis is poor; whereas, if the saturation increases above the resting value with

exercise the prognosis is favorable. The resting arterial blood oxygen saturation was poorly correlated with pulmonary function impairment.[6] A normal resting arterial blood oxygen saturation (96 per cent) has been observed to decrease 10 per cent with mild step-up exercise. Some persons who have subnormal oxygen concentration in arterial blood while at rest (even as low as 88 per cent) have increases of from 5 to 8 per cent upon exercise, a change brought about by the more uniform alveolar aeration accompanying the deeper breathing.[12]

Direct measurements of arterial pO_2 (Figure 2) provide a more sensitive index of early changes impairing the respiratory gas exchange than the arterial blood oxygen saturation (as determined from the content and capacity measurements), because the magnitude of the pO_2 changes is much greater and this greater range permits a better analysis of the specific factors producing impairment in the respiratory gas exchange. The effective inspired pO_2 varies with the barometric pressure and the proportion of oxygen in the inspired air. The average pO_2 sea level values of breathing air are: inspired, 150 mm. (mercury); alveolar, 100 mm.; arterial blood,

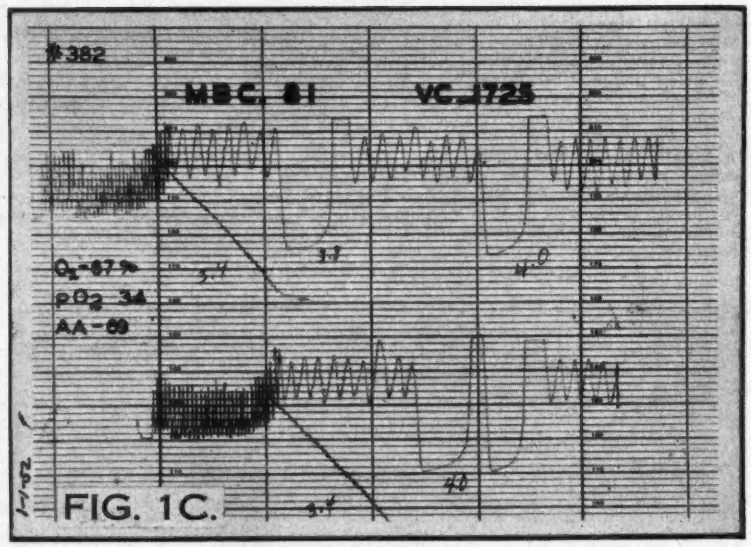


Figure 1-C.—A spirogram tracing of a very low vital capacity of 1,725 cc., but note that the entire volume was exhaled in three seconds; hence the effective vital capacity in this patient was actually higher than the 4,050 cc. shown in the abnormal tracing in Figure 1-B. The maximal breathing capacity was 81 liters per minute, indicative of a rapid exhalation. This tracing demonstrates the importance of recording the shape of the exhalation pattern by a rapid spirogram tracing, and that the three-second vital capacity is a much more significant measurement than the total vital capacity volume when the time factor is ignored.

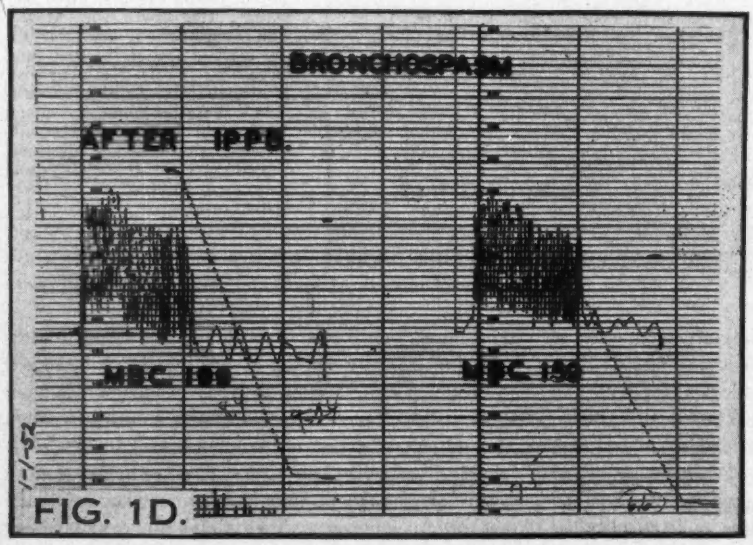


Figure 1-D.—Spirogram tracings of maximal breathing capacity in a normal person with a value of 159 liters before and 199 liters immediately after one treatment with intermittent positive pressure breathing and Vaponefrin.® Diagnosis: Chronic tracheobronchitis with bronchospasm secondary to postnasal discharge of chronic sinusitis.

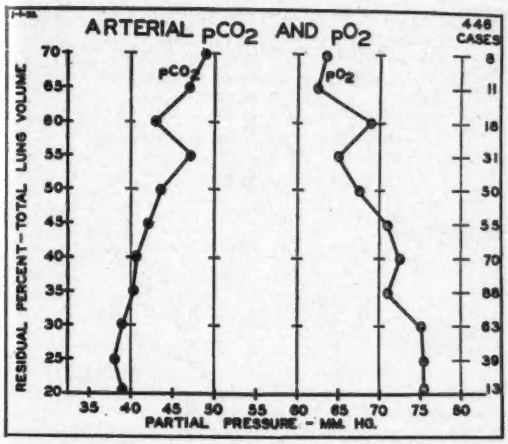


Figure 2.—Correlation between the residual percentage of total lung volume on the ordinate and the arterial pCO_2 and pO_2 partial pressures, in mm. of mercury, by direct determination in 446 cases of silicosis with fibrosis and emphysema. The individual points plotted for pCO_2 and pO_2 represent the average for the number of cases in each range of 5 per cent for the residual per cent of total lung volume (for example, 88 cases are represented with an average residual per cent of total lung volume of 35 per cent, plus or minus 2.5 per cent). It can be noted that when the residual percentage of total lung volume was greater than 35 per cent, the arterial pCO_2 was greater than 40 mm. of mercury, and this was increased progressively as the residual percentage of total lung volume was increased. The arterial pO_2 was decreased in the lowest group (residual 20 per cent of total lung volume) to 75 mm. of mercury (normal 100 mm. of mercury). The average pO_2 values were decreased progressively as the residual percentage of total lung volume was increased. A good correlation was found to exist between the increased arterial pCO_2 and the decreased arterial pO_2 with the increased residual percentage of total lung volume.

95 mm. If the expired air is collected at the same time as the arterial blood sample, the mean alveolar pO_2 can be calculated by the indirect method[18] (Figure 3) which assumes that the alveolar pCO_2 is the same as the arterial pCO_2. The mean alveolar pO_2 has been checked and reduplicated consistently by the indirect method in all types of patients with chronic pulmonary disease. Calculated arterial pO_2 values were found unreliable in studying patients with chronic pulmonary disease. In an analysis of 446 cases (Figure 3) the alveolar-arterial pO_2 difference was uniformly elevated independent of the residual per cent of total lung volume, but the alveolar pO_2 and inspired-alveolar pO_2 difference were correlated with the residual volume changes.

The distribution factor is the aspect most commonly involved, producing interference with the alveolar-arterial gas exchange in chronic pulmonary disease (Figure 4). Distribution refers to unequal alveolar aeration and perfusion, and the aeration factor concerns alveolar ventilation. At sea level the alveolar mean pO_2 is normally about 100 mm. of mercury, and blood perfusing alveoli will take up oxygen to a pO_2 level of about 95 mm. of mercury (normally saturated 96 per cent).

Alveolar aeration is impaired by loss of elasticity, fibrosis, obstruction from mucous plugs, secretions, partial atelectasis or depressed respiratory movement, as all of these conditions restrict the free movement of air in and out of the alveoli. Impaired alveolar aeration results in a lowering of the partial pressure of oxygen in the alveoli involved. Blood perfusing poorly aerated alveoli is incompletely saturated, but flows to the left side of the heart to mix with the normally saturated blood. The perfusion aspect of the distribution factor also includes those alveoli with complete aeration blockage but in which the blood supply is maintained. Such an alteration produces little shunts, there being no gas exchange in the blocked alveoli. Other alveoli may be ventilated but not perfused because the capillary blood supply is obliterated by fibrosis, thrombosis or vasoconstriction. The aerated but non-perfused alveoli represent physiologic dead space and decrease lung ventilation efficiency. The distribution factor has been found to be independent of the degree of pulmonary emphysema[6] (Figure 3).

The elevated mean alveolar-arterial oxygen gradient was decreased and the arterial oxygen saturation increased by intermittent positive pressure breathing using compressed air,[16] a response independent of the hyperventilation and increased blowing off of CO_2 produced by the respirators. The evidence from the intermittent positive pressure breathing data suggests that a more uniform alveolar aeration is accomplished by better inflation of those alveoli with impaired air circulation[13] (see Figure 4), partially correcting the interference produced by the mechanical obstruction resulting from fibrosis and the attendant loss of elasticity, often accentuated by bronchospasm. Some alveoli may be opened during intermittent positive pressure breathing which were totally closed during ambient breathing.

The per cent of oxygen removed from the air breathed in is a measure of the lung ventilation efficiency (normal 4 to 5 per cent at rest and 5 to 6 per cent during exercise, at sea level). For example, if the amount of oxygen removed from the air breathed is 4.5 per cent, then 45 cc. of oxygen is extracted from each liter of air breathed. If the amount of oxygen removed from the air breathed were greatly reduced, the volume of inspired air required would be proportionately increased for a given amount of work and oxygen consumption; hence, if the ventilatory measurements (MBC and vital capacity) are re-

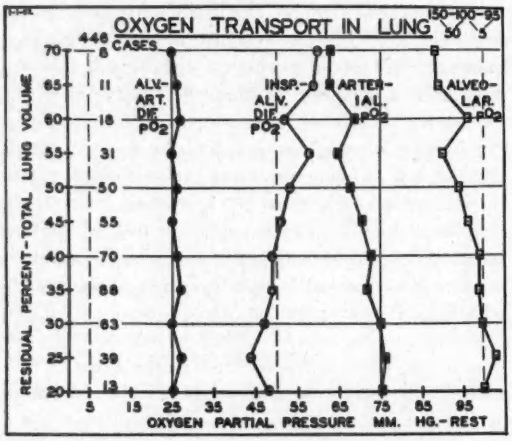


Figure 3.—The oxygen transport in the lungs was analyzed in the 446 cases referred to in Figure 2, using the same case grouping based on the residual per cent of total lung volume on the ordinate. The alveolar pO_2 was decreased progressively as the residual per cent of total lung volume was increased. If the residual was 40 per cent or more of total lung volume, the alveolar pO_2 was less than the normal value of 100 mm. of mercury. The arterial pO_2 values are parallel to the alveolar pO_2 changes. The difference between the inspired pO_2 and alveolar pO_2 was plotted in the same manner and correlated with the residual per cent of total lung volume. When the residual was 40 per cent or more of total lung volume, the inspired-alveolar pO_2 difference was greater than the normal sea level value of 50 mm. of mercury. The observed values less than 50 mm. of mercury resulted from hyperventilation when the residual was 35 per cent or less of total lung volume. An increased residual volume increases the difference between the inspired and alveolar pO_2, lowers the alveolar pO_2 and lowers the arterial pO_2 and the per cent saturation of the blood. When the alveolar-arterial pO_2 difference was plotted with the residual per cent of total lung volume there was no correlation. The average alveolar-arterial pO_2 difference was about 25 mm. of mercury, and this occurred in all of the groups, indicating the factor responsible for this gradient to be independent of the residual per cent of total lung volume. The alveolar-arterial pO_2 difference above was due to the distribution factor which is shown more graphically in Figure 4.

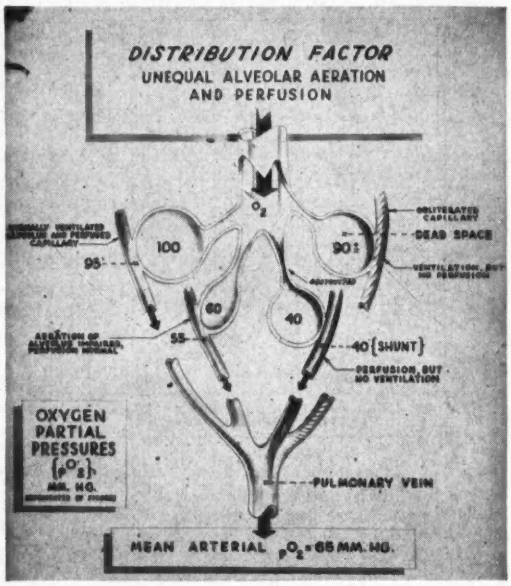


Figure 4.—A schematic diagram indicating the disturbed relationship between alveolar aeration and perfusion, as produced by pulmonary fibrosis, retained secretions, bronchospasm, emphysema, consolidation, pulmonary atelectasis or depression of respiration. Intermittent positive pressure breathing increases the effective pO_2 in alveoli with impaired aeration, but still perfused with blood, and increases the per cent saturation of the arterial blood. Intermittent positive pressure breathing has no effect on the oxygen transfer in alveoli which are perfused but non-aerated unless some alveoli are opened up by the increased inspiratory pressure. The distribution factor is characteristic of chronic pulmonary disease with fibrosis and emphysema.

duced, the individual may be unable to meet the elevated oxygen requirement. No correlation was found between the degree of pulmonary emphysema and the per cent of oxygen removed at rest (Figure 5), and only a slight average decrease with exercise. In most instances the lung ventilation efficiency was reduced, but this test as an isolated measurement was of limited value in estimating disability.[14]

The duration of dyspnea was determined subjectively after the step-up exercise test (30 steps on a stool 20 cm. high in one minute). This test is a practical one for pulmonary function, although not as a measure of physical fitness. Normal duration of dyspnea after the test is 90 seconds. Duration of dyspnea up to 120 seconds is a *slight* prolongation, from 120 to 180 seconds a *moderate* prolongation, and upward of 180 seconds *advanced* prolongation. When the ventilatory, residual air and arterial blood saturation measurements are essentially normal, prolonged dyspnea after the step-up test indicates increased pulmonary vascular resistance. A significant reduction in the expansibility of the pulmonary bed is indicated when the oxygen uptake is less than 400 cc. per square meter of body surface area during the one minute step-up exercise. Increased pulmonary vascular resistance especially during exercise is a factor in most cases of chronic fibrosis and emphysema, and is the primary factor in some cases as evidenced by the profound dyspnea after the one minute step-up test. Since the duration of dyspnea is a subjective test, the significance of a prolonged time requires careful evaluation in the individual case and is subject to the limitations of this type of test.

No correlation was noted between the degree of pulmonary emphysema and the circulation times obtained by either the arm to lung (ether) or arm to tongue (Decholin®) tests[14] (Figure 6). A pronounced

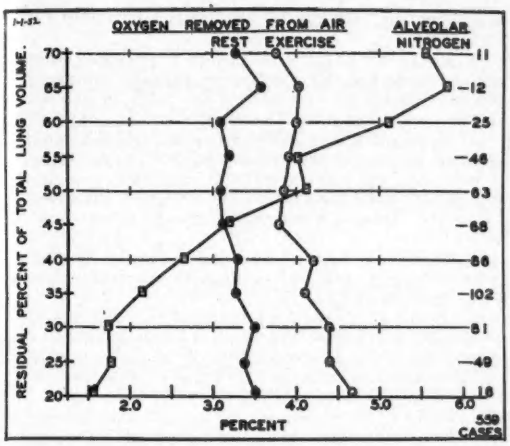


Figure 5.—The correlation between the per cent of oxygen removed from the inspired air both during rest and exercise and the residual per cent of total lung volume for 559 cases (as in Figure 2). The per cent of oxygen removed from the inspired air was decreased slightly at rest and during exercise as the residual per cent of total lung volume was increased. In contrast, note the good correlation obtained by plotting the alveolar nitrogen per cent after breathing 100 per cent oxygen for seven minutes with the residual per cent of total lung volume. The per cent of oxygen removed from the inspired air during rest and exercise (may be expressed as a ventilatory equivalent) was reduced some from the normal in most cases, but unless this value was very low it was not a significant factor in evaluating disability or pulmonary function.

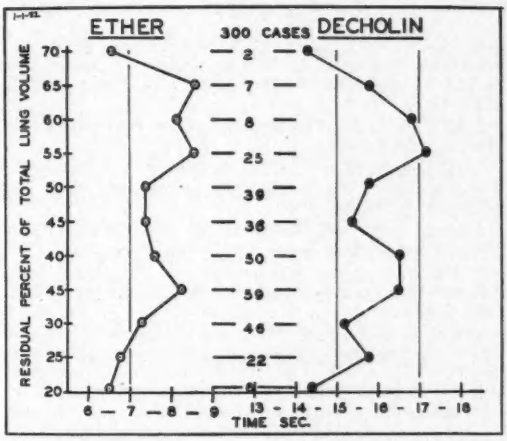


Figure 6.—The ether (arm to lung) and Decholin® (arm to tongue) circulation times correlated with the residual per cent of total lung volume in 300 unselected cases of fibrosis and emphysema. The number of cases for each group is shown in the center. There was no significant difference for either the ether or the Decholin circulation times with respect to the degree of emphysema as indicated by the residual per cent of total lung volume. If either the ether or the Decholin time were abnormally prolonged, a definite cardiac factor was indicated.

prolongation of circulation time indicated definite cardiac involvement.

Plasma volume studies in 138 coal miners with silicosis and respiratory complaints (using the Gregerson T-1824 dye method) revealed an increase of 10.2 per cent in the emphysema group and 5.4 per cent in the non-emphysema group[20] with an average packed cell volume of 42.4 per cent of the whole blood. The plasma volume was decreased slightly during treadmill exercise.

The average oxygen capacity in 115 cases of soft coal miners and 385 cases of hard coal miners was 19.48 volumes per cent (equivalent to 14.54 gm. of hemoglobin) with a standard deviation of 1.267 volumes per cent (0.95 gm. hemoglobin). There was no difference in the two groups of miners. Polycythemia is not a factor in coal miner's silicosis, even in cases of pronounced cyanosis and emphysema, in the absence of frank cardiac failure. An elevated hemoglobin content indicates cardiac failure, but not fibrosis and emphysema *per se*.

There was no apparent correlation between pulse and respiration rates during rest and exercise and the degree of impairment of pulmonary function[14] because of the wide standard deviation observed in each group.[14]

Dyspnea[19] is the most common complaint of coal miners with silicosis, a symptom resulting from fibrosis and/or emphysema. However, only 65 per cent of all coal miners studied had a significant degree of pulmonary emphysema (Table 2). Dyspnea commonly results from alteration in breathing resistance produced by increase in the air-flow velocity. This may accompany exertion or any other situation which actively increases pulmonary ventilation such as the acute hypoxia which may occur with lipiodol instillation.[15] Bronchial obstruction is an important factor producing increased breathing resistance in many cases. Bronchial obstruction[16] may be either permanently fixed or reversible in various degrees by inhalation of bronchodilator drugs. The reversible type is referred to as bronchospasm and the relief afforded by the bronchodilator drug is probably mostly from the relief of the bronchospasm, although the vasoconstrictor element may be of some importance. Bronchospasm occurs in normal persons during infection of the upper respiratory tract, but this temporary abnormality does not hamper activity, owing to the large breathing reserve present. Fibrosis with loss of lung elasticity tends to cause retention of secretions, enhances irritation of the bronchial mucosa and predisposes to bronchospasm with defective aeration of alveoli, especially in the lung bases in cases in which there is pronounced impairment of diaphragmatic movement.

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Funds for Medical Schools

THE SUM of $671,834 was turned over by the American Medical Education Foundation to the National Fund for Medical Education for distribution to the 79 medical schools in the United States. This represents the amount collected from physicians during the first six months of 1952. This money added to the amount collected from industry by the National Fund for Medical Education was distributed July 31 in the form of grants amounting to $15,000 to each of the 72 four-year schools and $7,500 to each of the seven two-year schools.

—A.M.A. News Notes

Operations on Large Arteries

Application of Recent Advances

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• With the use of anticoagulants to prevent recurrence of thrombosis it is now possible to open a major artery which has been occluded by a thrombus, remove the thickened lining with the clot and restore the continuity of the vessel. Free vein grafts have been used successfully to replace arterial segments in the extremities. Vein inlay grafts are preferred in dealing with aneurysms of the abdominal aorta. The aneurysmal wall can be used to support the venous segments.

It has been possible to by-pass aneurysms of the abdominal aorta by anastomosing the splenic artery to the left iliac artery. The use of the left superficial femoral artery as a by-pass to supply blood to the right leg is described.

AS WITH THE PROBLEM of duodenal ulcer, surgical operation is not the answer to the problem of arteriosclerosis but it may be of considerable value in the treatment of complications of that condition. Whereas previously the therapy of vascular disease was limited to conservative measures and helping the patient to adjust to disability or to amputation—confession of therapeutic failure—now, in many cases, it is possible boldly to attack the cause of the poor circulation, the diseased artery itself.

Experiments of Murray and Best[5] led to the use of heparin in connection with vascular operations, both general and regional,[3] and so overcame the greatest obstacle to successful operations upon blood vessels, namely, thrombosis. Now with the use of anticoagulants the incidence of successful restoration of continuity has been greatly increased.

In 1947 DosSantos[6] first reported upon his experience with thromboendarterectomy of a major artery. The success of this operation depends upon the fact that a line of cleavage is present between the viable portion of the blood vessel wall and the atheromatous plaque with the thrombus. Arnulf[1] used the term "sequestrum" to denote this obstructing material. After securing adequate control of the component arteries, the main vessel can be opened, the obstruction removed and the artery sutured. Anticoagulants have generally been used to prevent recurrence of thrombosis during the time required for a new intima to be formed. Although it is too early to evaluate this procedure from the standpoint of ultimate results (the first successful "sequestrectomy" of the abdominal aorta was performed in this country by Wylie[7] of San Francisco only 18 months ago) the immediate results are often remarkable and gratifying.

An example of this new operation is the case of a patient with occlusion of the abdominal aorta and iliac arteries associated with severe hypertension.

CASE 1: The patient, 46 years of age, gave a history of sudden onset of weakness in both legs nine years previously. Symptoms of hypertension had developed one year previously. In a preoperative aortagram (Figure 1, *left*) complete occlusion of the abdominal aorta and iliac arteries was noted. The collateral circulation to the pelvis and lower extremities was effected mainly through the superior hemorrhoidal branch of the interior mesenteric artery. There was also partial occlusion of the left renal artery. The blood pressure preoperatively was 210 mm. of mercury systolic and 100 mm. diastolic. Thromboendarterectomy of the aorta and iliac arteries was carried out. An organizing thrombus which partially occluded the orifice of the left renal artery was also removed. The patient made a splendid recovery

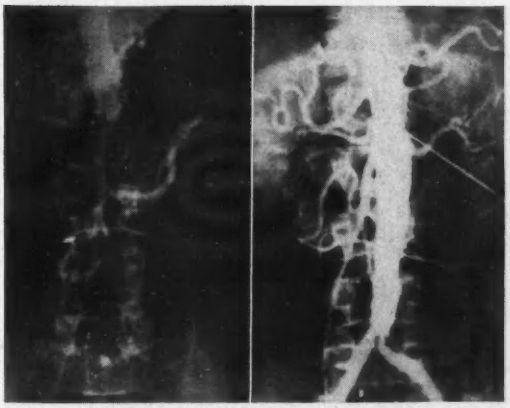

Figure 1.—*Left*, preoperative aortagram (Case 1). Complete occlusion of abdominal aorta and iliac arteries with partial obstruction of left renal artery. *Right*, aortagram following thromboendarterectomy, showing patency of the aorta, iliac, and both renal arteries.

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Part of a Symposium on Cardiac Surgery prepared jointly by the Section on General Medicine of the California Medical Association and the California Heart Association, presented before the Section on General Medicine at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

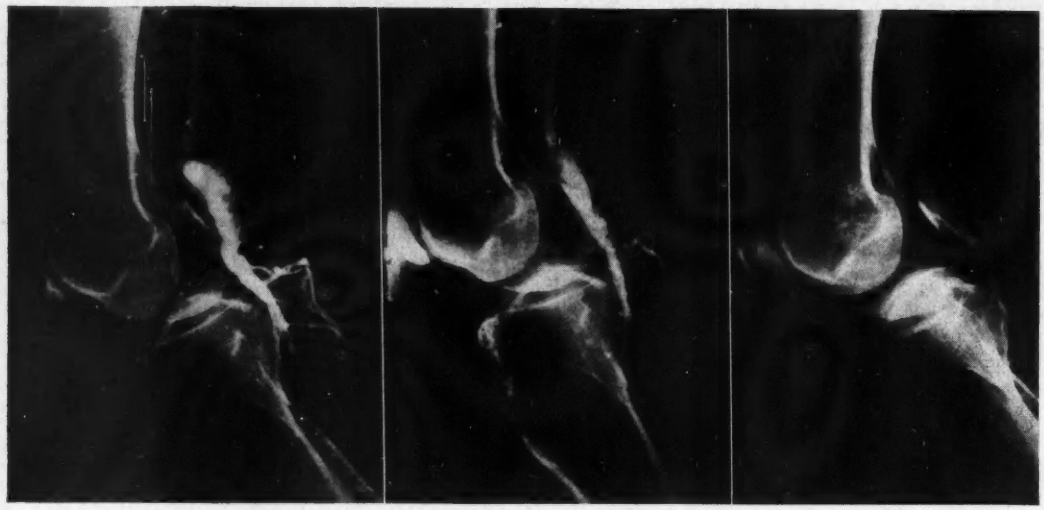

Figure 2.—*Left,* preoperative arteriogram of left popliteal aneurysm (Case 2) with early rupture. *Center,* two weeks after vein graft. *Right,* 18 months later. The calcification in the old aneurysmal sac was visible.

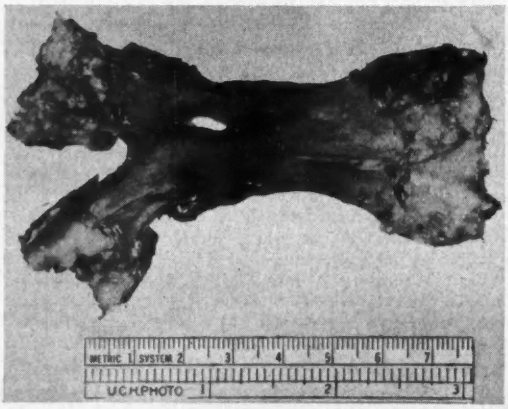

Figure 3.—Autogenous vein graft inserted into the terminal aorta of patient with an abdominal aneurysm. The rupture occurred ten hours postoperatively.

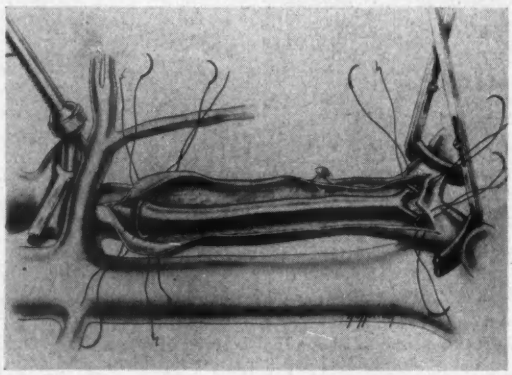

Figure 4.—Vein inlay graft of abdominal aorta using the left common iliac vein with its bifurcation.

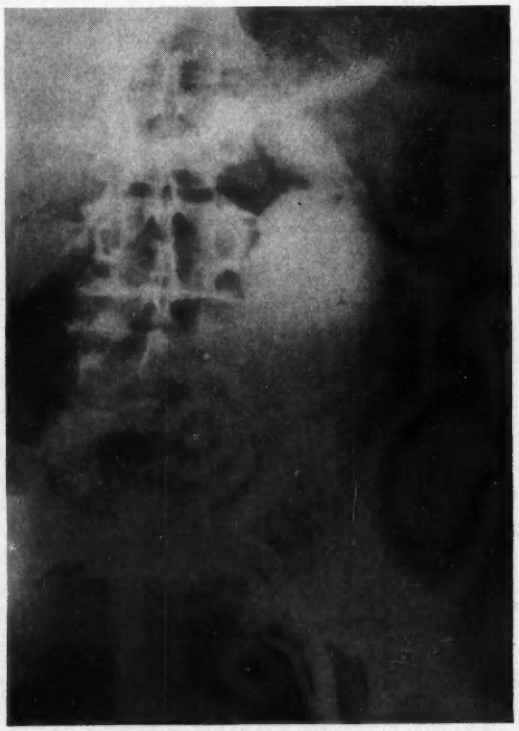

Figure 5.—A retrograde left femoral arteriogram, three months after operation, in a case in which continuity of the bifurcation of the abdominal aorta was restored by a technique in which the aneurysmal sac was used to support the venous segment. The patient was in good health 18 months after operation.

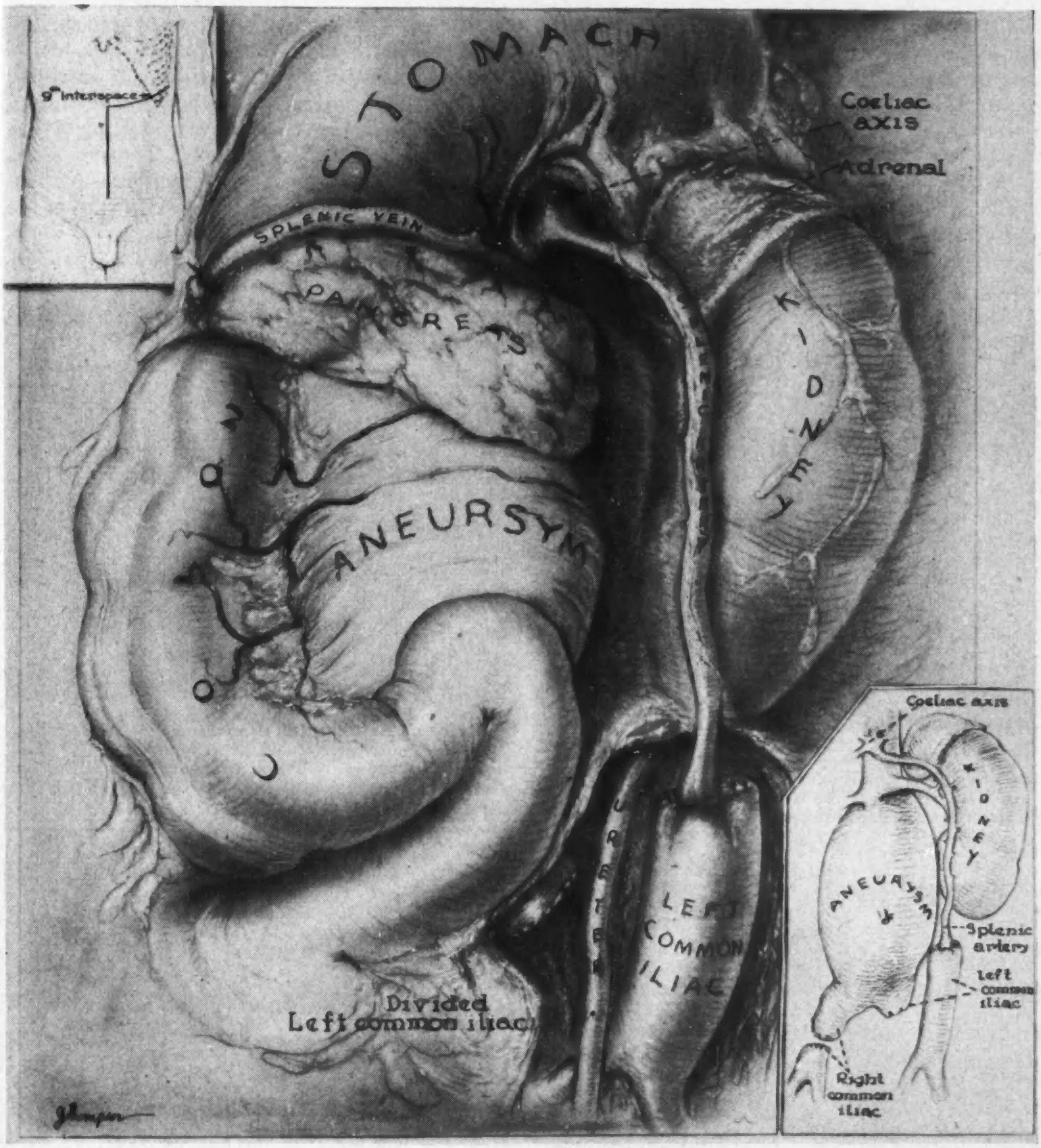

Figure 6.—Spleno-iliac arterial by-pass around aneurysm of abdominal aorta.

and, when examined three months after operation, had excellent circulation to both legs. The blood pressure was 120 mm. of mercury systolic and 72 diastolic. The postoperative aortagram is shown in Figure 1, *right*.

Vein grafts, both homologous and autogenous, have also been used to span the gap left by the removal of diseased arterial segments. The use of vein autografts in the surgical treatment of aneurysms has been sufficiently well established to permit brief reference. The dangers inherent in substituting a vein for an artery are not so great in the limbs where rupture need not necessarily lead to exsanguinating hemorrhage. The patient in the following case has been followed for a sufficient period of time to permit adequate evaluation.

Case 2: A man 69 years of age had a popliteal aneurysm which had started to expand and was causing pain. At operation a segment of the femoral vein was inserted to replace the section of diseased artery. In an arteriogram taken two weeks after operation the graft was observed to be patent, and 18 months postoperatively was still satisfactory (Figure 2).

In the treatment of abdominal aneurysms a free vein graft may be too hazardous. For example, the

fatal rupture of a segment of left common iliac vein with its bifurcation which had been inserted to replace the bifurcation of the abdominal aorta (Figure 3). The use of the aneurysmal sac to support the venous segment is illustrated in Figure 4. Within the past two years two patients have had successful restoration of the continuity of the bifurcation of the abdominal aorta by this technique. Figure 5 is an arteriogram taken in one of the cases. The patient was still in excellent health 18 months after operation.

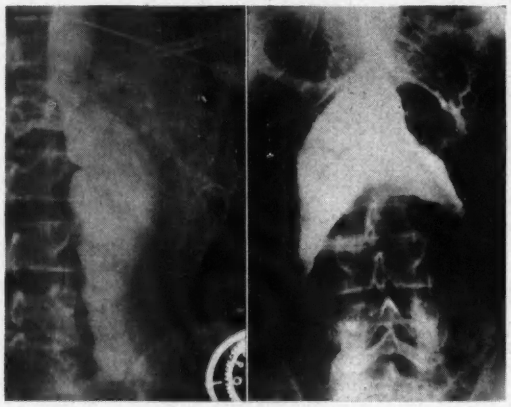

Figure 7.—*Left,* preoperative aortagram showing the large abdominal aneurysm. *Right,* postmortem study following fatal rupture of the left common iliac artery. The splenic artery can be seen partially filled just above the left renal artery.

Figure 8.—Preoperative aortagram showing thrombosis of abdominal aneurysm extending to the celiac axis and involving the iliac arteries. Circulation to both kidneys was maintained through collaterals.

The use of an arterial branch to by-pass the diseased segment was first utilized by Blalock and Park[2] in anastomosis of the left subclavian to the distal aorta in the treatment of coarctation of that structure. Lam and Aram[4] used a vein graft to by-pass an aneurysm of the thoracic aorta. The authors recently anastomosed the splenic artery to the left iliac in two cases to by-pass aneurysms involving the aorta and iliac arteries. Figure 6 illustrates the technique employed. The immediate result was satisfactory in the first case but the aneurysm ruptured three weeks after operation. The preoperative aortagram and the study made after death in this case are

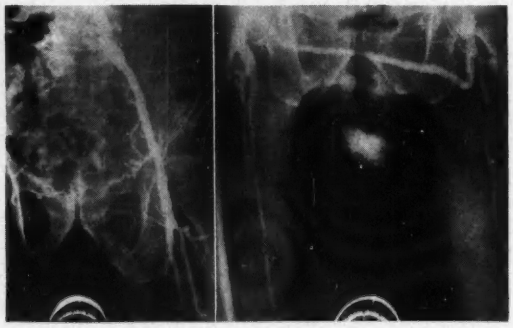

Figure 9.—*Left,* thrombosis of right iliac artery following thromboendarterectomy of left iliac artery. *Right,* arterial by-pass, left superficial femoral to right common femoral.

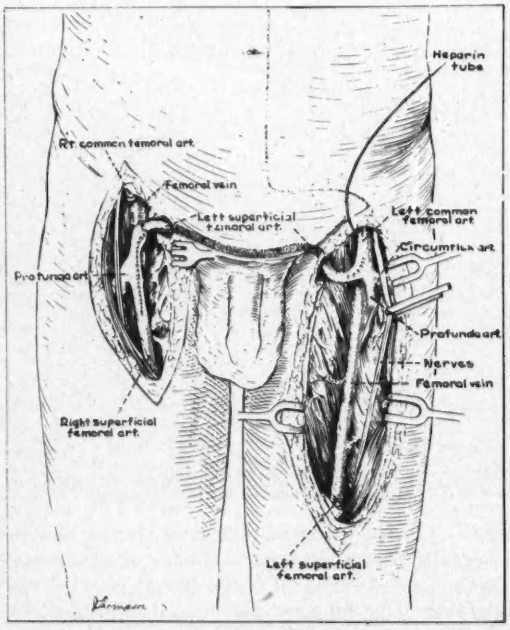

Figure 10.—Use of left superficial femoral artery to supply blood to right leg.

shown in Figure 7. This by-pass technique was successfully used later in a patient with a thrombosed aneurysm of the abdominal aorta. The thrombus had extended upward as far as the orifice of the celiac artery. The preoperative aortagram is shown in Figure 8. After anastomosis of the splenic to the left iliac artery the aorta was divided below the renal arteries, the thrombus removed with a uterine curette, the aorta sutured and the aneurysm removed. After stormy convalescence the patient made good recovery. The left femoral pulse was palpable and the circulation to the right leg was adequate.

Another by-pass operation for a peripheral artery is illustrated by the case of a patient who had severe obliterative arterial disease of both legs. At the time of left ilio-femoral "sequestrectomy," an aneurysm of the right iliac artery was noted. Cellophane was wrapped about this arterial segment. Six weeks later, thrombosis occurred with gangrene of the toes of the right foot. In an aortagram (Figure 9), occlusion of the right iliac artery was observed. The right superficial femoral artery, however, was observed in subsequent films to be open. In addition it was noted in the aortagram that the circulation to the left leg was being carried on chiefly through the profunda femoris, indicating that the left superficial femoral artery was probably obstructed. At operation it was found that the left superficial femoral artery was occluded at the adductor tendon. It was divided at this point (see Figure 10), the obstruction removed and, after transposition beneath the tissues of the abdominal wall, was sutured to the distal end of the divided right common femoral artery. After operation (Figure 9, *right*) the arterial supply to both legs was carried on through the left common femoral artery. The circulation to both feet remained excellent with separation of the gangrenous tip of the fifth toe.

It is fully recognized that operative intervention does not solve the main problem—arteriosclerosis—since this condition is generally widespread and operation is limited to the particular vessel involved. However, it does give promise of relief of some of the complications when the disease is limited to a single vessel.

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Infectious Allergy

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• The allergic reactivity which accompanies various infectious diseases is different in certain fundamental principles from the allergic disease associated with hypersensitivity to such agents as pollens, dust, and foods. Allergic sensitivity associated with tuberculosis comes about because of the participation of a fatty fraction of the bacillus with another component of the bacterium which is actually the sensitizing substance. The fatty fraction, if isolated from the bacillus, can act with various kinds of sensitizing substances that have nothing to do with tuberculosis to bring about the same kind of hypersensitivity that accompanies tuberculosis. Attempts are being made to learn more about the manner of action of this factor, and also to find out whether the organisms of other infectious diseases may have similar chemical constituents that cause allergic disease.

A GENERAL STUDY of various immunological facets of experimental tuberculosis which has been carried on in the Department of Bacteriology and Experimental Pathology at Stanford University during the past eight years led to the trail of tuberculous hypersensitivity, and subsequently into the bypaths of allergic sensitivity to other infectious diseases. From those investigations have come certain factual information and some speculation about fundamental factors that may be responsible for these hypersensitive states.

Bacterial allergic reactivity is a manifestation of the group of hypersensitivities termed "delayed," and these are distinguished by certain important characteristics from other hypersensitive states which are called "immediate" and which are exemplified by anaphylaxis, Arthus reactivity, and the atopic states. Differences between these two broad categories extend to the *induction* of the respective reactive states as well as to the *reactivity* of sensitized subjects.

With regard first to induction, it is well known that infectious hypersensitivity requires for its establishment the presence in the tissues of something in addition to the antigen responsible for it. In all instances in which the sensitizing antigen has been chemically isolated from an infectious agent this antigen acting by itself has been found inadequate for the induction of infectious hypersensitivity in normal subjects. Consequently, over the years it has come to be generally recognized that infectious allergic reaction cannot occur save in the presence of the infectious agent itself in the body, albeit this need not necessarily be living. In contrast, it is well known that any soluble or insoluble antigenic substance can give rise to the immediate type of hypersensitive state.

With respect to the reactivity of sensitized subjects, there are several features which distinguish these two states. First, the chronological sequence of events following the local or systemic application of antigen differs; from this fact, of course, the two categories have derived their names. Secondly, it is well known that humoral antibodies are intimately associated with the immediate hypersensitive state whereas no relationship between antibodies of blood or tissue fluids has been established for delayed reactivity. Consequently, delayed reactivity cannot be transferred to normal subjects by serum, while immediate reactivity can be so transmitted. (Certain cells, on the other hand, can transfer both forms of reactivity.[3,7,8,9,10]) Finally, the cellular responses in delayed hypersensitivity are more catholic than are those in the immediate type. So far as is known, all cells of the body with bacterial allergic sensitivity are capable of responding to the proper bacterial antigen; recent evidence indicates that this may extend even to the erythrocytes.[16] On the other hand, in immediate hypersensitivity the responsive units seem to be restricted to smooth muscle, blood vessel endothelium, collagen, and possibly mucus-secreting cells such as those of the respiratory tract. In a "geographical" sense of course this means that practically any part of the body may become involved in a hypersensitive response of the immediate kind, but the cellular basis for this is more limited than that which underlies delayed reactions.

These various differences provide criteria which may be applied to the controlled study of allergic reactivity. The factor of time necessary for the elicitation of the reaction, for example, provides a simple,

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but rather subjective, basis for distinction. A more objective ground is supplied by the study of the capabilities of humoral antibodies of the hypersensitive subject to transmit reactivity. Perhaps the best objective evidence, however, comes from a study of the cells able to react to exposure with antigen. If tissues from subjects with immediate reactivity are isolated for studies of this kind *in vitro* or if observations are carried out *in vivo* as has been done by Abell and Schenck,[1] it is observed that only those cells and tissues mentioned above visibly take part in the reactions to antigen. If, however, tissues without smooth muscle are explanted, then the circumstances are propitious only for the demonstration of the delayed form of reactivity, for in the absence of vascular elements or smooth muscle, nothing visible happens. If changes in collagen can occur in these circumstances, they have not been described. Studies of the reactions of cultures of bone marrow, spleen, and other tissues have consequently played an important part in the development of present knowledge of the reaction mechanism in hypersensitivity. The two photographs in Figure 1 illustrate the point. The picture on the left is of the bone marrow of a guinea pig which had been brought to a high level of anaphylactic sensitivity by the injection of protein obtained from the tubercle bacillus. (Any other soluble antigenic substance would have served as well for this demonstration.) The point is that this animal had pronounced Arthus reactivity to the intradermal injection of the protein and, several days before this fragment of tissue was taken, had pronounced anaphylactic symptoms following the injection of a minute amount of the antigen into the bloodstream. The photograph was made after the bone marrow cells in culture had been subjected to the presence of the protein for 24 hours. These cells are viable and motile; they are entirely unaffected by the presence of the antigen to which the animal itself was highly sensitized. In contrast, the photograph at the right reveals the situation under exactly the same experimental circumstances except that the bone marrow was removed from an animal sensitized to the tubercle bacillus. The allergic reactivity of this animal is directed against precisely the same protein of the bacterium, but in this case it is obvious that the cells of the marrow are so highly responsive to the presence of the protein antigen that death of most or all the cells has occurred.

An analogous but more simply performed objective criterion to permit the distinction between immediate and delayed hypersensitivity is furnished by the use of the cornea of the sensitized animal for observations of reactivity. As the cornea is without

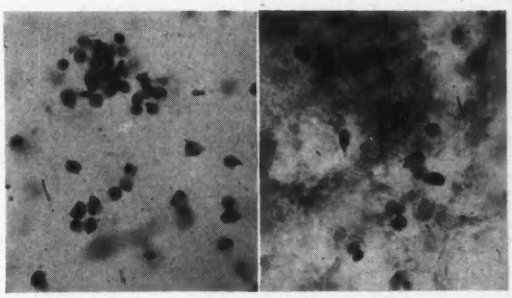

Figure 1.—*Left*—Bone marrow culture from guinea pig sensitized to tuberculoprotein. These cells have been exposed to the antigen for 24 hours and remain unaffected. (Hematoxylin and eosin stain, × 900.) *Right*—Bone marrow culture from tuberculous guinea pig after exposure to tuberculoprotein for 24 hours. Extensive cellular destruction has occurred. (Hematoxylin and eosin stain, × 900.)

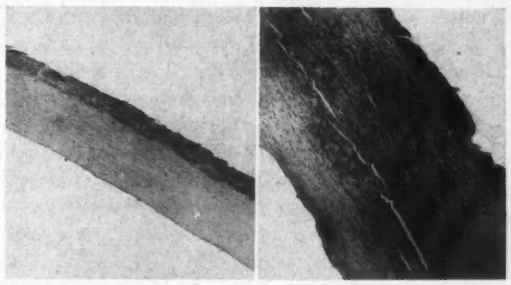

Figure 2.—*Left*—Cornea of guinea pig sensitized to tuberculoprotein. Forty-eight hours earlier a droplet of antigen had been injected, but no evident injury resulted. (Hematoxylin and eosin stain, × 85.) *Right*—Intense inflammation of cornea of tuberculous guinea pig 48 hours after injection of tuberculoprotein. (Hematoxylin and eosin stain, × 85.)

blood vessels or smooth muscle, it is incapable of entering into a reaction of the immediate type. If a small droplet of antigen is injected into the cornea of an animal with anaphylactic hypersensitivity and the tissue is observed for the following one or two days, no change is noted beyond the slight trauma incident to the injection itself. In contradistinction, an injection of the responsible antigen into an animal with delayed hypersensitivity leads, in 24 to 48 hours, to the development of striking keratitis. As is to be expected, if vascularization of the cornea is induced by treatment with some nonspecific irritant in advance of the test, then it is possible to evoke a corneal response in the anaphylactic animal also. Figure 2 illustrates these points. The photograph to the left in Figure 2 is of a section of the cornea of a guinea pig with a high level of anaphylactic reactivity to tuberculoprotein. The preparation was made two days after the injection of antigen into the cornea, and there was no detectable change in the tissue. In contrast to this, the

photograph to the right is of the cornea of an animal with delayed reactivity to the same antigen as the result of tuberculous infection; the reaction was intense and probably was accompanied by destruction of corneal cells. The two cases illustrated in Figure 2 are entirely analogous to the two illustrated by tissue culture photographs in Figure 1.

The allergic reactivity of tuberculous infection is amongst the most striking of the hypersensitive states accompanying infectious disease. It has been known for some years that the remarkable responsiveness which the body may develop to this bacillus is actually directed against the easily separated proteins of the organism. This fact was established upon a firm basis some years ago when Seibert[17] successfully crystallized a protein of the microbe and demonstrated its ability to elicit responses in tuberculous subjects, and it is substantiated daily through the use of purified protein derivative of the bacillus for clinical skin testing. Although this protein is a potent antigen its injection into normal animals does not eventuate in the development of the hypersensitive state characteristic of the disease itself. The humoral antibody response is good, and immediate hypersensitive reactivity of a high order becomes readily demonstrable in animals treated in this fashion.

For some years the question has been this: What distinguishes the antigenic activity of this protein as it exists in the body of the tubercle bacillus from that which it shows as an isolated substance?

Several years ago, during the course of experiments in which attempt was being made to evaluate the responses of the body to various isolated components of the tubercle bacillus as well as to the bacterial body deprived of various of its constituents, it was noted that animals which had been repeatedly inoculated with bacilli from which lipoidal substances had been extracted with ether, alcohol, and chloroform, did not become reactive to old tuberculin. This result was striking because it was apparent from the same experiment that the protein of these defatted bacilli had not lost its antigenic properties, since high levels of antibody developed in the treated animals and they became anaphylactically sensitized. In the same experiment, there were groups of animals which had received bacilli that had been only partially extracted; thus, one group had been treated with microbes from which only the ether-alcohol soluble substances had been removed, while another received organisms extracted only with chloroform. It was noted that the group which had received the ether-alcohol extracted bacilli became sensitized, while the animals vaccinated with the chloroform-extracted bacteria did not become sensitized. It was already known from the work of Anderson[2] that ether-alcohol removes phospholipids from the tubercle bacillus, whereas chloroform extracts a waxy substance composed principally of mycolic acid, a long chain fatty acid, alone and in combination with a carbohydrate. It appeared, then, that this waxy substance must be concerned in the induction of tuberculous hypersensitivity to the protein of the bacillus. This inference was soon substantiated by the injection into animals of the isolated lipoidal factor along with the isolated protein. This resulted in the establishment of hypersensitivity to tuberculin, and the delayed nature of this hypersensitivity could be demonstrated by all the various criteria which have already been described. No other combination of bacterial elements imitated this effect. Since that time the portion of the waxy lipid concerned in this activity has been more definitely delimited. It appears to be the mycolic acid-polysaccharide ester portion, but certain recent additional findings have suggested that perhaps something even simpler than this may be concerned, the chemical nature of which has not yet been ascertained.[11, 12, 13] Meanwhile, Choucroun who had also been engaged in work with bacillary fractions came to the conclusion that a factor which she termed Pmko is concerned in infectious hypersensitivity. This factor has been shown by her to be the mycolic acid-polysaccharide complex.[4, 5]

At Stanford, studies have been carried forward in two directions to investigate the possibility that the phenomena observed in connection with tuberculous hypersensitivity might also be present in other allergic conditions. First, it was of interest to know whether other antigens than the tuberculoprotein might serve along with the waxy lipid to induce the delayed type of hypersensitivity in animals. This was found to be the case with two antigens tested. one a well-known protein, egg albumin, the other a simple substance which has the capacity to induce contact reactivity when injected into the skin, picryl chloride. In the case of the albumin, it was found possible to establish hypersensitivity analogous in all respects to that obtaining in tuberculosis. With picryl chloride, contact reactivity was induced by means of intraperitoneal installation of the chemical along with the lipoidal element. Picryl chloride when injected into the peritoneal cavity alone does not act as an incitant of contact reactivity.[14, 15]

The other line of investigation has been concerned with the possibility that there might exist in infectious agents other than the tubercle bacillus a similar

relationship between a lipid and an antigen in inducing infectious allergy. For this purpose three organisms were chosen, one to represent the bacteria, one the viruses, and one the fungi. A group of C hemolytic streptococcus has served as the bacterium, vaccinia as the virus, and *Aspergillus niger* as the fungus. In each of these cases the allergy of infection reveals itself through tests with isolated proteins obtained from the respective agents. Some difficulty has been encountered in determining whether or not there may be a lipoidal factor analogous to that of the tubercle bacillus in these various agents, but so far evidence has been elicited that this may be the case in the streptococcus and the virus, although it is not conclusive enough to warrant publication of details. Results of work with the fungus cannot yet be interpreted.

Since these phenomena began to come to light, one concern of the investigators has been the question of the mechanism through which the lipoidal factor may modify the body so that it responds with delayed hypersensitivity to a protein antigen. So far as can be determined, the lipoidal factor itself has no antigenicity. The reactivity of the body is directed, as was mentioned previously, against the protein. The lipoidal factor possesses the ability to induce the formation of epithelioid and related cells, and it has been thought that these may be associated with the infectious hypersensitive response of the body. However, other portions of the bacillus which are not concerned in this hypersensitivity can also call forth such cells. It has been assumed that the lipoidal factor may in some way modify various cells so that they are more amenable to the entry of antigens than they would ordinarily be. For the purpose of studying this point, the tuberculoprotein used has been marked by the introduction of a bright colored dye into the molecule, in the hope that it might thus be possible to trace the distribution of antigen in the body under the influence of the waxy factor. So far the method has given no clue to support the hypothesis, but this may be owing to fault in the technique rather than to error in the hypothesis. It is difficult to see this dye in small amounts in the tissue. For this reason attempts are being made to trace the antigen by using a fluorescent compound such as is being employed by Coons[6] for studies of the distribution of antigens in the body.

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Leukemia

Duration of Life in Children Treated with Corticotropin and Cortisone

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• *The average duration of survival of 15 cases of childhood leukemia treated with corticotropin and cortisone was 6.8 months. This survival was the same as observed among 59 children who received no treatment, or treatment with x-ray, or blood transfusion alone.*

Despite the fact that objective evidence of remission was observed in 7 of 15 children treated with corticotropin and cortisone, the remissions were not reflected by a longer duration of life.

Treatment of childhood leukemia with corticotropin and cortisone appears to be a palliative measure, without significant effect on the duration of life.

IN THE THERAPEUTIC trials of corticotropin (ACTH) and of cortisone for neoplastic diseases, particular interest and emphasis have been manifested in their use in children with leukemia.[2, 3, 4] A recent summation[4] recorded the experience from eight clinical research centers. Of 218 children with leukemia treated with corticotropin or cortisone either alone or in combination with other therapy, 98 or 45 per cent were reported to have had objective evidences of clinical remission of the disease. The length of the remissions was from one to ten weeks. When subsequent courses of hormonal therapy were given, only a few of the patients had beneficial responses.

Few reports have emphasized the duration of life in patients treated with these hormones. This information would appear to be crucial for the evaluation of the effectiveness of the agents in leukemia, whether such evaluation is used for research or for practical therapeutic purposes.

In the present study of fifteen children with leukemia treated with corticotropin and cortisone it was noted that although there was objective as well as subjective evidence of clinical improvement, these manifestations were not reflected in a statistically significant prolongation of life.

PATIENTS AND METHODS

The diagnosis in all cases was supported by at least two examinations of aspirated bone marrow and by classical clinical and hematologic symptoms.

Corticotropin (adrenocorticotropic hormone or ACTH) and cortisone (17-hydroxy-11-dehydrocorticosterone)† were administered intramuscularly, usually in divided doses at 6- to 8-hour intervals. The daily dose varied from 25 mg. to 300 mg. Courses of ten days or more were followed by a rest period of seven to ten days before the alternative hormone was instituted.

All patients were on a low-salt diet (less than 1.0 gm. of sodium chloride per day) to prevent edema, and when practicable supplemental oral potassium chloride was administered to avoid hypokalemia. Supportive therapy with both antibiotics and blood transfusions was used in 12 of the 15 cases.

Examination of the patients, as well as determination of the content of hemoglobin, erythrocytes, leukocytes and platelets in the blood, was carried out at least twice a week, and more often when indicated. Studies of the chemical constituents of the blood were performed only for the proper care of the patient.

Table 1 presents the relevant data regarding the 15 children. Fourteen died, and autopsies confirming the diagnosis of lymphoblastic leukemia were available in 12. One patient (Case 4), who was alive more than two years after onset, had mild generalized adenopathy, and the predominant abnormal lymphocytes in the peripheral blood and bone marrow aspirate were consistently of the small, mature type. During the second year of the disease a few cervical nodes were enlarged and the spleen was barely palpable. The case must be considered one of chronic subleukemic lymphogenous leukemia.

Of the 14 patients who died, five (Cases 2, 3, 7, 12 and 14) were subleukemic during the course of the disease. Five patients (Cases 6, 9, 10, 11 and 13) had frank leukemia, with leukocytes numbering 20,000 to 500,000 per cu. mm. of peripheral blood. Four patients (Cases 1, 5, 8 and 15) had both leukopenia and leukocytosis during the course of illness.

From the Laboratory of Experimental Oncology, National Cancer Institute, National Institutes of Health, Public Health Service, Federal Security Agency and the Division of Medicine, University of California School of Medicine, San Francisco.

†Obtained from the Armour Laboratories and Merck and Company, respectively, through the National Institutes of Health.

TABLE 1.—*Effects of Corticotropin and Cortisone in Children with Leukemia.*

Case	Sex	Age	Duration Prior to Course (Mos.)	Hormone	Total Dose (Mg.)	Days Treated	Previous Therapy	Antibiotics	Blood Transfusions	Subjective Improvement	Decreased Spleen Size	Decreased Adenopathy	Decreased Liver Size	Decreased Fever	Decreased —Leukemic Cells— Peripheral	Decreased —Leukemic Cells— Bone Marrow	Increased Platelets	Duration of Effects (Wks.)	Survival from Onset (Mos.)
1.	M	1.5	1	Cort.	1,650	36	....	Yes	2	*	*	*	*	*	*	*	*	7	
			3	ACTH	1,050	18		....	....	*	*	0	0	0	†	0	—	2	
			4	Cort.	250	10		....	....	*	0	0	0	—	—	0	0	—	
			5	ACTH	625	13		Yes	2	—	—	—	—	—	—	—	—	—	6.0
2.	F	11	4	ACTH	1,700	14	....	....	2	*	—	—	—	*	—	—	0	—	
			5	Cort.	1,700	14		Yes	4	*	*	*	*	*	*	*	0	16	
			8	ACTH	1,700	14		Yes	....	*	—	—	—	0	—	—	0	—	
			9	Cort.	1,400	14		Yes	5	*	—	—	—	—	—	0	0	—	11.0
3.	M	3	2	Cort.	1,025	11	....	Yes	2	*	*	*	*	0	*	0	†	2	
			2.5	ACTH	600	12		Yes	....	*	0	0	0	0	*	0	†	2	
			3	Cort.	375	11		Yes	....	*	0	0	0	*	—	0	—	—	
			3.5	ACTH	350	15		Yes	....	—	—	—	—	*	—	0	—	—	
			4	Cort.	700	7		Yes	3	—	—	—	—	—	—	—	—	—	5.0
4.	M	2	5	Cort.	1,550	31	....	Yes	....	0	0	*	0	0	—	†	0	—	
			6.5	ACTH	500	10		....	....	*	0	0	0	0	—	—	0	—	
			7.5	Cort.	600	14		....	....	0	0	0	0	0	—	—	0	—	
			8.5	ACTH	350	14		....	....	0	0	0	0	0	—	—	0	—	living
			9.5	Cort.	900	21		....	....	0	0	0	0	0	—	*	0	—	(24.5+)
5.	M	3	5	Cort.	1,775	31	Amino-	Yes	3	*	*	*	*	*	—	*	†	4	
			6	ACTH	550	18	pterin	....	....	*	—	—	—	0	—	0	—	—	
			7	Cort.	150	6		Yes	3	†	—	—	—	*	—	0	—	—	
			8	Cort.	1,000	10		Yes	2	—	—	—	—	—	—	—	—	—	8.5
6.	M	4.5	1	ACTH	625	7	....	Yes	4	*	*	*	*	*	*	0	0	2	2.5
			1.5	Cort.	425	8		Yes	....	*	*	*	*	*	*	—	0		
7.	M	2	0.5	ACTH	675	15	....	....	....	*	*	0	0	0	0	—	—	—	
			1.0	Cort.	600	14		....	....	*	0	0	0	0	0	0	—	—	3.5
8.	M	16	8	ACTH	300	2	....	Yes	18	*	—	—	0	*	—	0	—	—	9.0
			8	Cort.	2,950	18													
9.	F	3	0.5	ACTH	1,430	42	....	Yes	10	*	—	—	—	—	—	—	—	—	4.0
10.	M	11	1.5	ACTH	1,700	14	....	Yes	1	*	*	—	*	*	*	0	†	2	
			2.5	Cort.	400	4		Yes	3	—	—	—	—	—	—	—	—	—	2.5
11.	M	5	2	ACTH	4,700	28	Chicken-	Yes	1	*	*	*	*	0	*	*	*	5	
			4	Cort.	2,275	25	pox	....	2	*	—	—	—	—	*	—	—	—	6.0
12.	M	3	1.5	ACTH	1,000	10	....	....	3	—	—	—	—	*	—	—	—	—	2.0
13.	F	5	6	ACTH	900	8	Melamine	Yes	1	—	—	—	—	0	—	0	—	—	6.5
14.	M	2	7.5	ACTH	187	4	....	Yes	3	—	—	—	—	—	—	—	—	—	7.5
15.	M	4	2.5	Cort.	1,150	14	X-ray	Yes	3	*	†	—	—	*	—	—	—	—	3.0

Symbols: * = definite effect; † = equivocal effect; — = no effect; 0 = not present or not determined.

Three patients were treated for leukemia with other agents before hormonal therapy was given. One of them (Case 3) received a course of aminopterin (4-aminopteroyl-glutamic acid) one month before treatment with cortisone. Another (Case 13) had had three courses of trisethylene melamine (trisethylene-imino-*s*-triazine), and one (Case 15) had had two courses of roentgen therapy necessitated by the presence of a large mediastinal mass that embarrassed respiration.

In Case 6, the patient was treated with 5 mg. of nitrogen mustard (methyl-bis-betachloroethyl amine) after completion of the hormone therapy, also because of a mediastinal mass. The excellent clinical remission in Case 11 was observed following the onset of chickenpox; the hormones were used primarily in an attempt to prolong the remission presumed to have been due to the acute infectious disease.

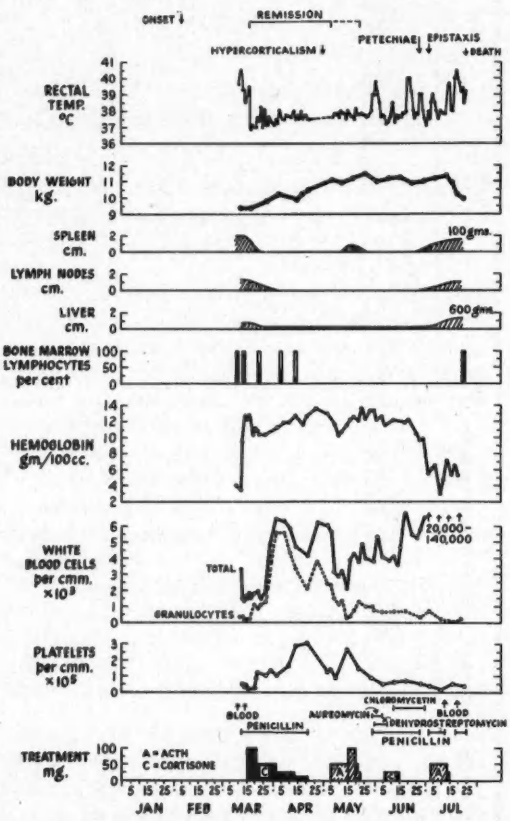
RESULTS

Subjective improvement during hormone therapy was observed in 12 of the 15 patients. Evidence of such improvement included more normal activity, expressions of a sense of well-being, reduced irritability, and better general appearance. This was accompanied by a great increase in appetite, to be anticipated with the use of the agents, and reduction of temperature to normal levels in nine cases.

Objective evidence of clinical improvement was observed in seven patients. Such evidence included significant and sustained reduction in the size of the spleen, liver and lymph nodes, and a significant decrease in the absolute number of leukemic cells in the peripheral blood and/or the bone marrow with a concomitant rise in the normal blood elements. A pronounced increase in the number of platelets was observed in two patients, and a slight transient rise in three others.

The typical, almost complete remission in Case 1 is detailed in Chart 1. A dramatic drop in temperature and reduction in the size of spleen, lymph nodes and the liver occurred within a week after the initiation of treatment with cortisone. There was a rise in the number of granulocytes in the peripheral blood, and, somewhat later, in the number of platelets. At the same time, the number of lymphoblasts and abnormal lymphocytes in the bone marrow dropped from 98 per cent to 25 per cent of the total number of leukocytes. The effects were sustained for approximately seven weeks, and were partially achieved for another two weeks following the second course with corticotropin. Subsequent hormonal therapy was without avail, and leukemic leukocytosis and hemorrhagic diathesis developed. The total duration of the disease, from clinical onset, was six months.

CHART 1



Results of treatment with cortisone and corticotropin in the case of an 18-month-old boy with lymphogenous leukemia.

The beneficial effects in five patients were transient, lasting two to four weeks. In two patients the remissions lasted five and sixteen weeks, respectively. Favorable response was noted in three of six patients with subleukemic disease, in three of five patients with frank leukemia, and in one of four patients who had both leukopenia and leukocytosis during the course of the illness.

The initial course of treatment was with cortisone in five cases, with three remissions, and with corticotropin in ten cases, with four remissions. In the plan of treatment these two agents were used alternately, with a rest period of seven to ten days between courses. Thus, nine children received a second course of the hormones; of four patients treated with corticotropin, two had remissions, but no further remissions occurred in five patients that received a second course with cortisone. Five children, including four who had responded to the first course of treatment, received four courses of the two hormones, but no

remissions were observed with either the third or the fourth course.

During the course of treatment the usual signs and symptoms of hypercorticalism were observed in ten of the fifteen children. These consisted of rounding of the face, and enlargement of the abdomen. Edema of the extremities was noted in these patients, and was controlled by reduction in the dose of the hormones, further decrease of sodium intake and supplementation of potassium chloride. Transient elevation of blood pressure developed in two patients. None of the complications was serious.

The mean survival of all fifteen patients after the onset of symptoms attributable to the disease, including the single patient still living, was 6.8 ± 1.4 months. If the patient with chronic leukemia is not considered, the mean survival was 5.5 ± 0.9 months. The median survival, as determined by interpolation of the graphed data on all fifteen patients, was 4.8 months. Survival among seven patients who responded to treatment was from 2.5 to 11 months, and the average was 5.9 months. Survival among seven patients who had no objective response was from 2 to 9 months, and the average 5.1 months. Excluding the five patients who received x-ray or radiomimetic chemicals and the patient who had chickenpox, the mean survival of the remaining nine patients was 5.6 months.

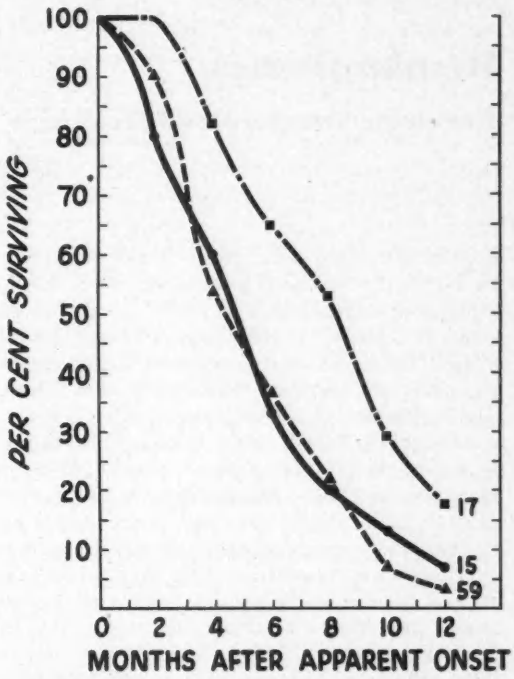
DISCUSSION

The results relative to duration of life in this group of patients were compared with a previous base-line study on the duration of life in 76 children with lymphogenous leukemia.[1] In that study it was noted that among 59 patients who received no treatment, or treatment with x-ray or blood transfusions only, the mean survival was 5.8 ± 0.5 months. Among seventeen patients who were treated with both antibiotics and blood transfusions, the average survival was 8.9 ± 1.2 months, a difference significant at the 2 per cent level. One of this group survived for 23 months; if this case is excluded, a mean of 8.0 ± 0.8 months is obtained. This mean is significantly different from the mean of the group of 59 cases at the 1 per cent level.

The survival of fifteen children treated with corticotropin or cortisone was 6.8 ± 1.4 months, or 5.5 ± 0.9 months if the patient with chronic leukemia who is still living is not considered. Neither of these means is significantly different from the mean of the 59 patients. If the mean on 14 children is compared with the mean on 16 children treated with antibiotics and blood transfusions, but excluding the case of longest survival, a difference significant at the 1 per cent level is obtained (5.5 ± 0.9 against 8.0 ± 0.8).

These data are graphically presented in Chart 2. It

CHART 2



Duration of life in children with lymphogenous leukemia. Square dots, 17 children treated with antibiotics and blood transfusions; triangular dots, 59 children treated with x-ray, blood transfusions or receiving no treatment; solid line, 15 children treated with cortisone and corticotropin.

is quite clear that the duration of life in children with lymphogenous leukemia treated with corticotropin and with cortisone is the same as in the children who do not receive these agents. The clinical remissions, therefore, are not reflected in a longer duration of life. Since 12 of the 15 children who received the hormones also received antibiotics and blood transfusions, it could have been anticipated that the duration of life would have been closer to the mean of 8.9 months than the 6.8 months actually observed.

The analysis of the results on this small group of patients indicates that the effects of corticotropin and of cortisone in childhood leukemia were palliative, and that the duration of life was not increased by the use of these hormones.

Laguna Honda Home.

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Hemangiomas

Histologic Structure, and Treatment

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• *Hemangiomas are considered tumors originating in blood vessels and are classified as ectatic and hyperplastic. Controversy regarding active therapy occurs in the case of strawberry hemangiomas which are hyperplastic capillary hemangiomas. Although they may clear up spontaneously, on rare occasions they may predispose to grave sequelae. Port-wine stain hemangiomas should never be treated with x-ray or radium.*

HEMANGIOMAS are blood vessel tumors which may be the result of ectasia of preexisting vessels, a combination of ectasia and new growth, or new growth alone. It is because of differences in origin that the clinical and histological characteristics of these tumors vary and therefore call forth the many therapeutic measures advocated for eradication.

Ectatic tumors of blood capillary origin are known by the term *hemangioma simplex*. Such tumors may be either arterial (Figure 1) or venous (Figure 2) in origin, and either congenital or acquired. The congenital ones are the nevus flammeus (port-wine stain). At times they may involve the internal viscera and when associated with hemorrhages they have been designated as Rendu-Osler Weber's syndrome. Capillary cutaneous angiomas of the congenital ectatic type sometimes are associated with congenital neural anomalies such as the syndrome in which there is associated tuberosclerosis, Sturge-Weber's syndrome in which there is encephalofacial angiomatosis, and Lindau-von-Hippel's disease in which there is hemangiomatosis of the retina and brain.

Acquired ectatic capillary angiomas include the lesions designated as spider nevus or nevus araneus. They occur in women during pregnancy and even though they are extensively disseminated, they frequently disappear spontaneously after parturition. In both sexes they occur with liver disease such as cirrhosis. Exposure to below-freezing temperatures has occasionally been considered the cause of angiokeratoma of Mibelli, in which condition there is a keratoma overlying the ectatic capillary hemangioma occurring on the extensor surfaces of the lower extremities. Occasionally, capillary hemangiomas resemble pigmented nevi in clinical appearance, especially when they are on the mucocutaneous border of the lower lip where they appear as blue-black rounded macules (Figure 3).

Whether congenital or acquired, ectatic capillary hemangiomas are histologically the same. The papillary cutis and the papillary bodies are replaced by large numbers of dilated congested blood capillaries. These vessels lie directly beneath the epidermis. The vessel walls of these capillaries consist of a single layer of mature endothelial cells whose nuclei are elongated and flattened with their long axes running parallel with the long axis of the capillary. In nevus flammeus, associated with tumor formation, the ectasia of the blood vessels extends also into the reticular or deeper cutis.

The ectatic blood vascular tumors of larger vessels are classified under the term *hemangioma cavernosum* (Figures 4 and 5). As was previously noted, they may be associated with hemangioma simplex. These lesions are clinically bluish in color, and frequently are found not only in the skin but also in mucous membranes and internal organs such the tongue and liver. The most extreme type of congenital cavernous hemangioma is seen in the systemic hemangioma *unius lateralis*, in which an entire extremity becomes hypertrophied to elephantiastic size. The acquired cavernous hemangiomas include varicose veins, which might be based on hereditary vascular inferiority. Ectasia of larger blood vessels is also seen in inflammatory disease of the skin which is followed by loss of elastic tissue and atrophy—acrodermatitis chronica atrophicans. Cirsoid or racemose hemangiomas are arteriovenous fistulas which are characterized by pulsation, bruit, and alternate change of color from red to blue. Lesions of this type, when they occur on a lower extremity and are accompanied by ulceration, are sometimes mistaken for varicose veins and ulceration.

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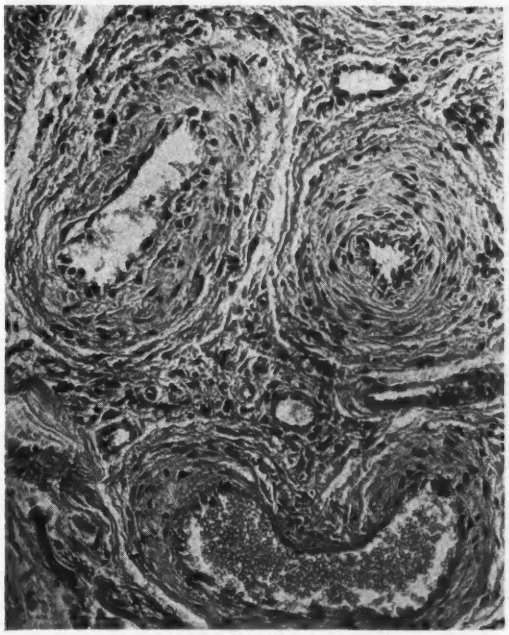

Figure 1.—Hematoxylin- and eosin-stained section (reduced from × 220). Ectatic capillary hemangioma of arteriolar origin. The endothelial cells are mature and flattened on the lumen of the vessels.

Figure 2.—Hematoxylin- and eosin-stained section (reduced from × 220). Ectatic capillary hemangioma of venous origin. The endothelium of the capillaries is flattened against the capillary walls. Large amounts of blood are in the vessels.

Histologically, in cavernous hemangioma not only is there ectasia of the larger vessels but, sometimes, perivascular fibrosis of varying degree depending on duration, on frequency of trauma and on the amount of manipulation. The smaller lesions appear to be surrounded by connective tissue almost to the extent of capsule formation. The larger, older lesions contain dense and thick fibrotic bundles of connective tissue between the ectatic congested blood vessels. At times this connective tissue appears to be almost hyalinized. The blood channels anastomose with each other and resemble the spaces in a sponge cut across. They are always congested and contain blood clots in various stages of thrombotic organization and recanalization.

Hypertrophic hemangiomas or strawberry birthmarks are present at birth or develop shortly afterward. They are not only the most common congenital hemangiomas but also the most common congenital tumors of infancy and childhood. They occur most frequently on the head, neck, and face at the sites of embryonal fissures and have therefore also been called the fissural angiomas.

Histologically hypertrophic hemangiomas consist of great numbers of dilated, closely aggregated capillaries with well formed endothelial walls (Figures

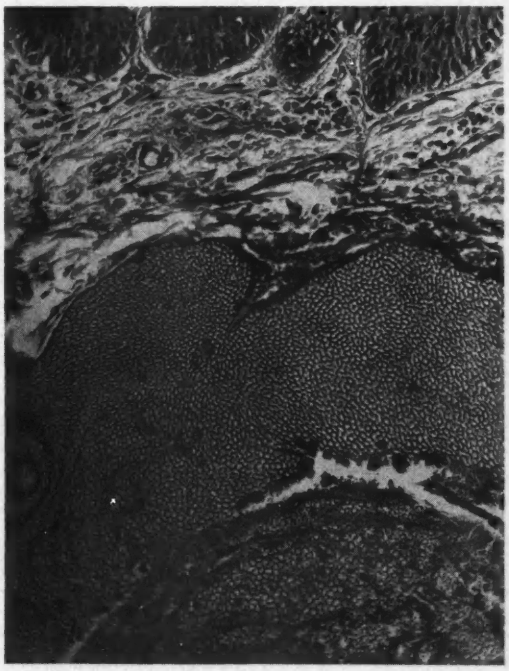

Figure 3.—Hematoxylin- and eosin-stained section (reduced from × 220). From a thrombotic ectatic vein on the lower lip. The endothelium is flattened against the vessel wall.

Figure 4.—Hematoxylin- and eosin-stained section (reduced from × 60). A cavernous hemangioma with involvement of the entire cutis. The vascular spaces are lined by a single layer of endothelium. Thrombi are seen in the lower portion of the section.

Figure 5.—Hematoxylin- and eosin-stained section (reduced from × 220). A higher-powered magnification of Figure 4. The endothelium is one layer thick and is flattened along the vascular lumen.

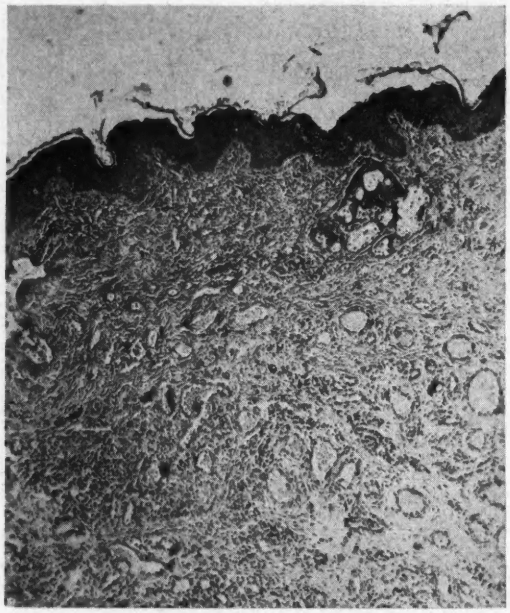

Figure 6.—Hematoxylin- and eosin-stained section (reduced from × 60). A hypertrophic capillary hemangioma (strawberry type). Numerous capillaries and cellular masses involving the entire cutis.

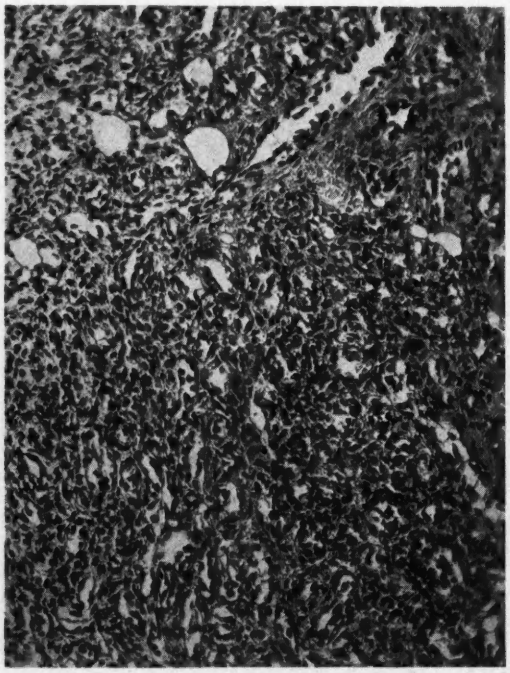

Figure 7.—Hematoxylin- and eosin-stained section. Mature capillaries adjacent to immature capillaries and solid cords of endothelium are seen. The immature endothelium consists of large globular hyperchromatic nucleated cells with vacuolated cytoplasm.

Classification of Hemangiomas (Arterial and Venous)

ECTATIC		HYPERPLASTIC
Capillary (Spider Bursts)	Larger Vessels	Capillary (Strawberry Type)
Acquired:		
1. Liver disease	1. Mechanical: Varicose veins	1. Infectious: Pyogenic granuloma
2. Pregnancy	2. Inflammatory disease: Acrodermatitis chronica atrophicans	2. Traumatic: Sclerosing angioma
3. Traumatic	3. Traumatic arteriovenous anastomosis	Hemangioendothelioma
Congenital:		
1. Nevus araneus	1. Cavernous hemangioma	1. Hypertrophic capillary (strawberry birthmark)
2. Nevus flammeus (port-wine)	2. Systematized angioma unius lateralis	2. Hemorrhagic sarcoma
	3. Racemose or cirsoid	3. Hemangiosarcoma

6 and 7). There is a delicate tissue stroma between these endothelial walls. There are solid cords of endothelial cells adjacent to the well formed capillaries. In some of these solid cords, vacuolization of the endothelial cells, with a tendency toward canalization of the solid cords, may be observed. The endothelial cells are large and have large globular nuclei whose long axis is vertical to the long axis of the vessel walls. The large size of the nuclei and the vacuolization of the cytoplasm together with the presence of solid cords of endothelial cells is indicative of the immature hyperplastic nature of the lesion. Deeper areas in the cutis contain the more mature and ectatic blood vessels very suggestive of cavernous hemangioma.

THERAPY

As is indicated by the histologic structure of mature endothelium of the capillaries in hemangiomas simplex and cavernous hemangiomas, many therapeutic means that will affect these structures will also affect the adjacent structures as well as the overlying skin. In this category, except for the spider nevus which can readily be destroyed by electrocoagulation or electrolysis, ectatic capillary angiomas of port-wine type are best left alone.

Cavernous hemangiomas and hypertrophic capillary hemangiomas are difficult to differentiate, especially when they occur together. Clinically and histologically it is difficult at times to differentiate pyogenic granuloma (infectious hemangioma) in infants from hypertrophic capillary hemangioma (strawberry birthmark). This confusion is further increased by the fact that hemangioendothelioma may resemble both of these two conditions. Thus, a vascular hyperplasia of congenital origin may be simulated by one of infectious origin as well as by one of neoplastic origin.

Nodular subepidermal fibrosis is occasionally designated as a sclerosing angioma (Figures 8, 9 and 10). This is based on the premise that the vascular origin and structure of the lesion are indicated by stain showing the reticulum arrangement around the vascular core of the lesion. It could be the prototype for the neoplastic hemorrhagic sarcoma of Kaposi which shows proliferation of the same elements: blood capillaries and connective tissue. Not infrequently early lesions of Kaposi's sarcoma are diagnosed as hypertrophic capillary hemangioma or even as pyogenic granuloma by clinicians and pathologists. Auken,[1] in a report on progressive multiple angiomas, cited a case in which the lesion was erroneously diagnosed as incipient hemorrhagic sarcoma of Kaposi. Frequently pyogenic granulo-

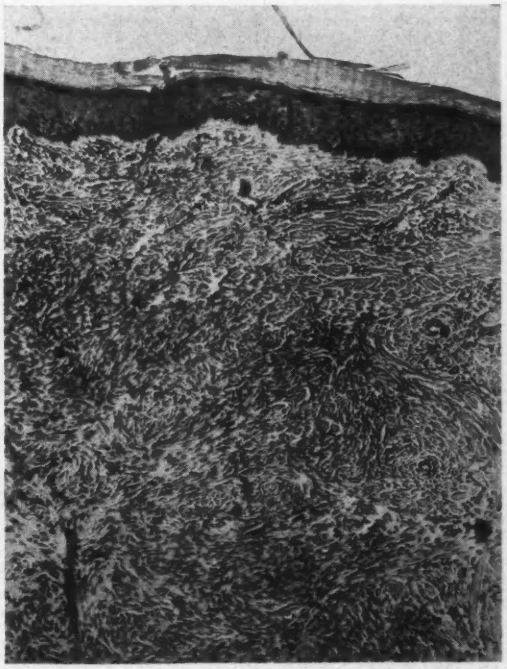

Figure 8.—Hematoxylin- and eosin-stained section (reduced from × 60). Sclerosing hemangioma involving the middle and lower cutis.

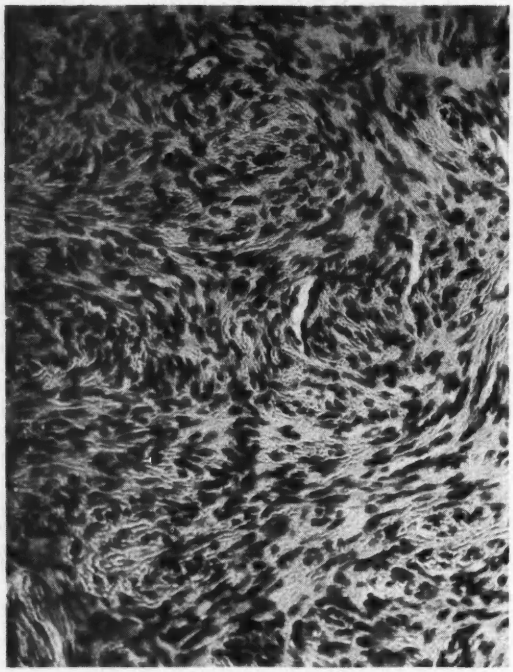

Figure 9.—Hematoxylin- and eosin-stained section (reduced from ×220). The fibrotic fasciculi surrounding capillary spaces in which the endothelium protrudes in the vessel lumina.

Figure 10.—Reticulum stained section (reduced from ×220). Sclerosing hemangioma with the reticulum arranged around the vascular core of the lesion.

mas, sclerosing angiomas, and lesions of Kaposi's sarcoma are removed after they have been diagnosed clinically as melanoma. Ewing and Powell[3] reported that in 8 per cent of a series of cases in which pigmented skin lesions were removed upon clinical diagnosis of melanoma, the lesions were later proved to be sclerosing angiomas.

Hypertrophic capillary hemangiomas are known to undergo spontaneous regression on occasion, either due to the tumor's own growth shutting off its blood supply or some minute trauma causing necrosis of the embryonic endothelial cells, which rapidly undergo fibrosis. This reaction can at times result in ulceration and severe hemorrhage.

Ectatic hemangiomas of capillary nature (except for those appearing during pregnancy) and cavernous hemangiomas may reach a certain size and then grow no more, or they may become progressively larger, in some instances until they are inoperable and result in death.[5] In some instances small cavernous hemangiomas have been permitted to grow until they were not only unsightly but also interfered with function, as in the case of a 14-month-old child with cavernous hemangioma of the upper lip that interfered with eating.[4] Hemangioendotheliomas also sometimes have been permitted to grow until major procedures were necessary. It is necessary, therefore, to begin treatment as soon as possible. Costello[2] stated that the best results were obtained when treatment was begun before the patient was three months of age. The younger the lesion, the smaller it is and the more sensitive to treatment. The possibility of malignant metaplasia of hemangiomas must be kept in mind, for untreated hemangiomas of bone may become malignant in later years.

Injection therapy of cavernous hemangiomas, whatever be the sclerosing fluid, is at times necessary for lesions on the tongue and in the nasal sinuses. It has also been advocated by Pack and Miller[6] as a preoperative procedure in cavernous hemangiomas to reduce hemorrhage at operation. Injection of a cirsoid hemangioma with sclerosing solution and similar therapy for the dilated veins of acrodermatitis may cause necrotic ulcers. Injection therapy of hemangiomas does not necessarily require intraluminal injection. It is at times safer and just as effective to inject the sclerosing solution into the perivascular spaces, thus setting up an inflammatory process which causes fibrosis and resulting obliteration of the endothelial spaces by the sclerotic connective tissue.

The only objection to the injection therapy is the temporary indurated and tender mass which it creates and which is at times quite alarming to the physician and to the parents of the patient. Advantages of

the injection therapy are that it eliminates the necessity of damaging the overlying skin and it can be used for both cavernous and hypertrophic capillary hemangiomas.

Ectatic congenital capillary hemangiomas of diffuse nature ("port-wine stain") are best left alone. The abrasive therapy advocated by some physicians may cause development of a silica granuloma later. The tattooing of pigment into the spaces between the epidermis and the dilated capillaries has not as yet given the satisfactory results hoped for. Single ectatic capillaries are best destroyed by either electrolysis with monopolar Oudin current or microcautery. Punching the lesion out with a cutaneous punch one or two millimeters in diameter and pulling the edges of the wound together with fine suture is also an effective method.

Radiation with either radium or roentgen ray is the simplest, least difficult and least painful of the therapeutic measures that can be used to treat hypertrophic capillary hemangiomas (strawberry birthmark). Use of radium plaques, or tubes, properly filtered and administered by one who has had experience with them is the treatment of choice in lesions that do not lie above vital areas. Radiation therapy is contraindicated for telangiectatic hemangiomas because the dosage required to cause sclerosis is sufficient to cause radiation sequelae such as keratosis, atrophy, and carcinoma. Radiation therapy is also contraindicated for lesions over bony epiphyses, breasts, and genitalia because of the inhibition of growth of bones and breast and the sterilizing effect of the rays on the genitals. Lesions of the scalp should be treated very cautiously with radiation therapy because of possible permanent alopecia.

Superficial coagulation with solid carbon dioxide, liquid air and even microcautery are very satisfactory for superficial hypertrophic capillary hemangiomas. Surgical excision is advocated for all lesions unsuccessfully treated by other more conservative procedures and where there is active growth. Surgical operation is the only method of treating systemic hemangiomatosis and cirsoid hemangiomas.

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ACKNOWLEDGMENT

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Vitamin U Therapy of Peptic Ulcer

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• *Vitamin U, administered as raw cabbage juice to 100 patients with peptic ulcer, was apparently effective in promoting the rapid healing of uncomplicated peptic ulcers. The evidence of therapeutic benefit was (1) the rapid relief of the symptom, pain, without the use of any set plan of symptomatic treatment, and (2) ulcer crater healing time (determined roentgenographically) considerably shorter than in groups of cases, reported in the literature, in which "standard" types of diet and drug therapy were employed.*

RESULTS of a number of animal experiments carried out in the medical research laboratories at Stanford University School of Medicine in the past ten years[1, 2, 3, 4] indicate that a dietary factor plays some role in the etiology of peptic ulcer. Certain raw foods, particularly green vegetables, contain some substance, termed vitamin U, which prevented the development of histamine-induced peptic ulcers in guinea pigs. This substance is readily destroyed by heat, and may be rapidly destroyed by oxidation. The therapeutic use of vitamin U in the form of cabbage juice in the treatment of a group of thirteen patients was reported in 1949,[5] and a further report dealing with the clinical use of this form of therapy was made in 1950.[6] The present report consists of an analysis of the therapeutic effect of vitamin U in cabbage juice on the healing of peptic ulcer in 100 patients (including the 13 originally reported upon) who were treated in a period of two and one-half years.

SELECTION OF PATIENTS FOR TREATMENT

At first only patients were accepted for this form of treatment who had a readily demonstrable ulcer crater and who were free from such complications as recent bleeding, pyloric obstruction and long-standing symptoms suggesting extensive cicatricial changes. Since many patients who did not meet these qualifications requested cabbage juice therapy, it was decided to accept all patients for vitamin U therapy who had a clearly established diagnosis. In accepting a number of patients with complications, it was recognized that some patients in this group might not be expected to respond satisfactorily to any form of medical therapy, and that operation might be necessary.

Also it was obvious that improvements in the patient's condition as measured by the time required for an ulcer crater to heal as observed in serial x-ray studies[5] would not serve as a satisfactory criterion in all cases because a crater in the duodenum could not always be demonstrated clearly and the progress of a complicated case could not always be followed a sufficient length of time to judge crater healing time accurately. Consequently in a number of cases symptomatic relief of ulcer pain had to serve as the sole criterion of improvement.

As most patients were hospitalized during the first seven to fourteen days of treatment, bed rest alone may have contributed to the development of well-being in some instances. Each patient received only cooked (heated) food in the diet during the period of experimental therapy[6] and no routine standardized administration of drugs was permitted. However, in the first few days of treatment, drug therapy was used when absolutely necessary for relief of pain or restlessness. Relief of abdominal pain by vitamin U therapy was only judged to have occurred when the use of symptomatic drug therapy was not required and when pain no longer appeared spontaneously. All patients were required to take one quart of fresh raw cabbage juice daily, in four or five divided feedings,[6] or a dehydrated form of cabbage juice. Fifteen patients received the dried material which was prepared by lyophilization and assayed for antipeptic ulcer potency.[4] It was mixed with enough water (one-half the original bulk of fresh juice) to permit complete solution. A few patients were unable to take large amounts of fresh juice consistently. Juice therapy was continued until pain was relieved and the ulcer crater as observed in x-ray studies (when available) had completely disappeared. In some instances the period of therapy was one week, in most 10 to 21 days.

Whenever possible x-ray examinations to determine ulcer crater healing time were carried out at

[*Dr. Cheney's manuscript is not printed here in entirety. Tables giving details of clinical and roentgenographic observations in each of the 100 cases were deleted to save space. The more detailed information will be included in reprints of the article, available from the author.*]

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7- to 14-day intervals. However, some patients with clearly demonstrated ulcer craters declined follow-up x-ray studies when they were symptomatically relieved. If an interval of a month or more elapsed between x-ray examinations, it is obvious that crater healing time could not be accurately calculated. Ideally x-ray studies should be done weekly. In all cases, blood examinations (cell count, Kahn test and sedimentation rate determination), stool examination, and fractional alcohol gastric analysis were carried out. Some of the patients with gastric ulcer were also examined with a gastroscope.

ANALYSIS OF 100 PATIENTS

All but five of the 100 patients either were under the care of the author or were treated under his direction and all records were available to him. There were 74 men and 26 women 21 to 78 years of age and the average age was 49.5 years. Seventy-two patients were hospitalized for treatment and 28 were treated at home. Twenty-five patients treated at home were ambulatory, the majority of them working.

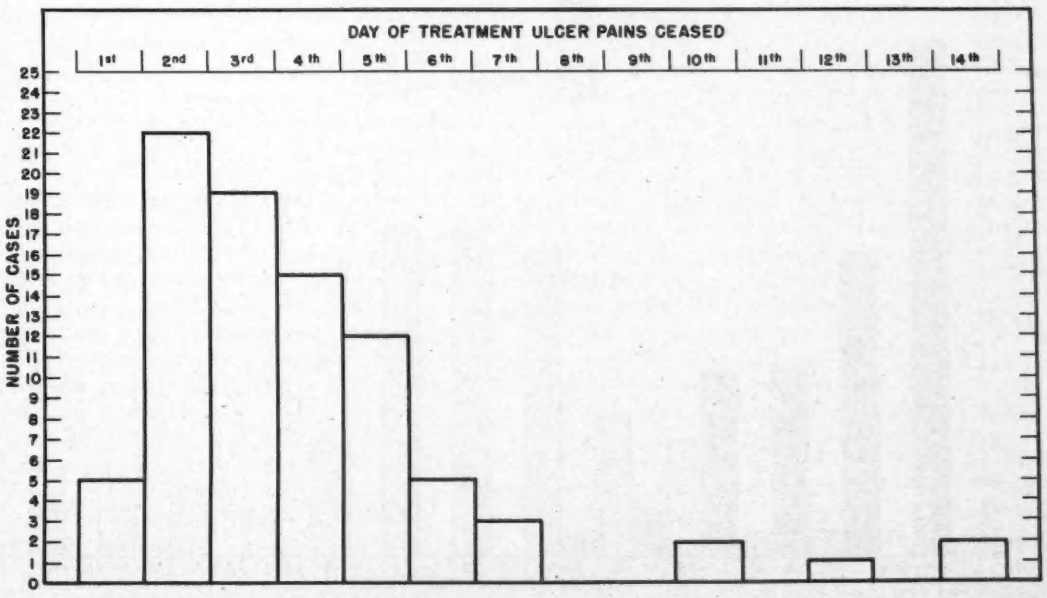
The location of the ulcer was in the stomach in 25 cases, in the duodenum in 71 cases and in the jejunum (marginal or submarginal) in 4 cases. In 55 cases there were enough satisfactory roentgen films to permit determination of ulcer crater healing time. In 17 of these cases the lesion was in the stomach, in 36 in the duodenum and in 2 in the jejunum. In one case there was a peptic ulcer crater in both the stomach and the duodenum. In 17 cases in which the diagnosis of duodenal ulcer was established by clinical and x-ray observation no constant ulcer crater outline could be demonstrated. Ulcer craters that were visualized by x-ray in profile as a niche were measured in their greatest diameter and in their maximum depth. Ulcers that could be visualized only *en face* were measured in their greatest diameter. Lesions varied in diameter from 0.2 cm. to 3.0 cm. and in depth from 0.3 cm. to 1.5 cm.

RESULTS OF VITAMIN U THERAPY

Appraisal of improvement was based first on relief of pain, and second on ulcer crater healing time. As eight patients were pain-free at the time therapy was begun (these patients had ulcer craters clearly visible by x-ray examination), there were 92 patients suitable for study of pain relief. Eighty-six of them (95.9 per cent) were pain-free within two weeks, and 81 per cent of the total were symptom-free within one week. The day of pain relief for the 86 patients is shown in Chart 1. Sixty-one of the patients were pain-free within four days. The average time from beginning of therapy to relief of pain in the 86 cases was 3.92 days.

In 19 cases no ulcer crater could be clearly demonstrated. In 17 of those cases a diagnosis of duodenal ulcer was established and in 2 a diagnosis of jejunal ulcer. Twenty-six of the 81 patients with clearly demonstrable ulcer craters could not be suf-

CHART 1



Time of relief of pain after beginning of therapy in 86 of 100 patients with peptic ulcer treated with raw cabbage juice. Six were unrelieved (see text). Eight did not have pain at time therapy was started.

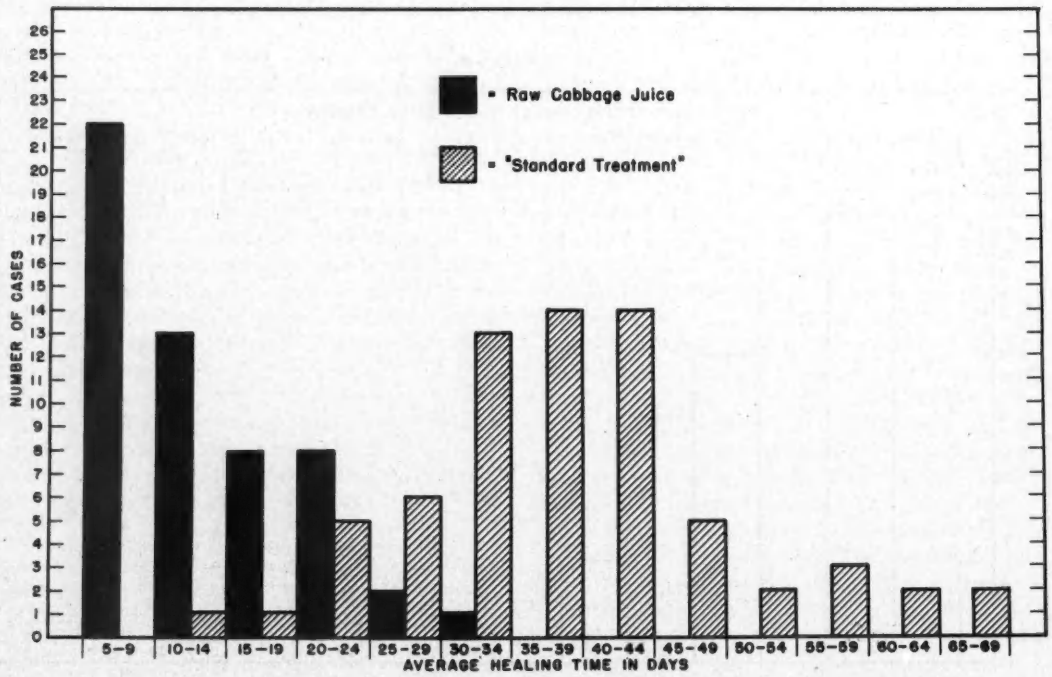
ficiently well followed to determine crater healing time. In the remaining 55 cases crater healing time was determined.

In the 17 cases of gastric ulcer in which healing time was determined, it varied from 6 to 27 days; the average time was 14 days.

As to the eight cases in which crater healing time could not be calculated by x-ray examination: Three patients had no follow-up x-ray study after 6 days, 7 days, and 21 days of therapy. However, the first and second of the patients were operated upon promptly and in both instances after gross and microscopic examination the gastric ulcers were described as benign and healing. The third patient was symptom-free after the third day. In five cases there was no significant reduction in size of the ulcer after 5, 8, 9, 10, and 29 days of treatment. One of the five patients had polycythemia vera, and, in examination of sections of the stomach in the region of the ulcer crater removed at operation, extensive thrombotic changes of the vessels which apparently reduced the blood supply to the involved area were noted. Inadequate circulation could easily have retarded healing. In another case, in which operation was done on the tenth day after treatment was started, a large benign ulcer had perforated into the pancreas. In a case in which the ulcer crater was 1.0 cm. by 0.3 cm., the lesion was observed to be healed when x-ray examination was carried out three months after treatment ceased, but as the last preceding roentgen study had been done on the sixteenth day of treatment, the crater healing time could not be estimated. It was somewhere between one and four months. A patient in whom no reduction in the ulcer niche was observed upon x-ray examination after eight days of therapy, was operated upon on the eleventh day and at that time epithelialization of the ulcer was noted. A patient with a pyloric lesion and partial obstruction was under direct observation for only ten days, but was known to be improved and working one year later.

Although there were 54 cases of duodenal ulcer with crater in the series, only 36 of them were suitable for analysis of crater healing time (Chart 2), including one case in which the crater was no longer visible in the only follow-up x-ray study, 32 days after the beginning of therapy. Another case was not included because the patient was chronically ill and had a lesion in the pancreas. Although no definite crater was observed in this case at an x-ray examination after 72 days of therapy, upon subsequent x-ray examination six months later a large crater in

CHART 2



Crater healing time in 54 cases of peptic ulcer treated with raw cabbage juice, compared with healing time in 68 cases (reported in the literature) in which "standard treatment" was given.

the duodenal cap was noted; and, at operation, penetration of the ulcer into the pancreas and a localized small chronic pancreatic abscess were observed. For the 36 cases of duodenal ulcer in which healing time was determined, it varied between 6 and 32 days and averaged 12.9 days.

In seven of the seventeen cases in which crater healing time could not be calculated there was no satisfactory follow-up x-ray examination. Six of the seven patients felt well and declined further x-ray study. Improvement was noted in four patients who were last examined by x-ray after nine to ten days of treatment, but the crater was still present. All four were symptom-free. One patient who still had an ulcer crater eighteen days after therapy was started was operated upon, and a duodenal ulcer perforating into the pancreas was observed. In two cases in which ulcers still were present, as determined by roentgen study after ten days of treatment in one instance and after 21 days in the other, the patients apparently had not been adequately treated: they had received a preparation of lyophilized cabbage juice which, when it was fed to guinea pigs that received repeated injections of histamine,[4] gave little prophylactic protection against peptic ulcer. Late follow-up studies of three patients with unhealed ulcers could not be obtained.

Seventeen patients with duodenal ulcer without crater all had a "typical deformity" of the duodenal cap with tenderness and irritability of the cap. Three of them were pain-free at the time they were treated, but 12 of the 14 with pain became symptom-free. The two who did not were treated for such short periods (three days and five days) that satisfactory therapeutic results could hardly be expected. In five cases no follow-up x-ray studies were made, including the two cases mentioned in the preceding sentence. In the other three of the five cases symptomatic relief occurred within two days of the beginning of cabbage juice therapy. In eight of twelve cases, improvement in the "indirect findings" of duodenal ulcer was noted in follow-up roentgen studies, and in four there was no change. Two of the latter four patients were originally pain-free, and the other two became pain-free during therapy. As far as can be judged from the data presented, this group of seventeen patients did as well as could be expected from any known form of medical treatment.

In considering the therapeutic results in the four cases of jejunal ulcer, it would appear that this type of peptic ulcer would benefit from vitamin U therapy. A favorable result might be expected on the basis of the generally accepted concept that the mucosa of the small intestine (jejunum and ileum) is lacking in some factor which normally affords a high degree of resistance to acid-pepsin digestion of the gastroduodenal mucosa. This expectation seems to have been borne out, as the average crater healing time in the two cases of jejunal ulcer adequately studied by x-ray was 10.1 days. The average healing time for the total series of 54 cases with demonstrable peptic ulcer craters which could be satisfactorily followed by periodic x-ray examinations was 13.1 days, or just under two weeks.

DISCUSSION OF THERAPEUTIC RESULTS

The results of treatment of 100 patients with peptic ulcer indicate that therapy with vitamin U in the form of cabbage juice deserves careful consideration and further study. Although an exactly comparable series of cases for a comparative analysis was lacking in the present study, it should be taken into consideration that 84 per cent of the patients treated had had symptoms of peptic ulcer for one month or longer before receiving cabbage juice and that at the time vitamin U therapy was begun nearly all of them were under some form of treatment which had already proven unsuccessful as regards sustained symptomatic relief. A number of the patients, and 21 additional "control patients" that were given "standard" treatment for ulcer had been examined initially by x-ray and again thirty or more days later without demonstrating disappearance of an ulcer crater. Consequently, although ulcer crater healing time could not be accurately calculated in these cases, it could be said that it exceeded one month in all instances, and was considerably longer than the average time of 13.1 days obtained in the series of patients treated with vitamin U.

In considering that the symptom of pain was relieved in 86 per cent of the patients treated with cabbage juice, and that the average length of time from beginning of therapy to relief of pain was four days, it might well be stated that in this series the interval before relief of pain was similar to that which has been reported for almost all other forms of therapy, nearly all of which involve the use of a bland diet, alkalis, sedatives, antispasmodics and, not uncommonly, a variety of old or newly introduced drugs. By that standard alone, the best that could be said for the effectiveness of vitamin U therapy in relieving pain is that it is only as good as many other forms of treatment. However, there is a very important and significant difference. Relief of pain occurred in this series of cases without the continued use of any form of drug therapy and without frequent feedings of food. This is in sharp contrast to experience in the usual series of peptic ulcer cases reported in which the symptoms are obliterated or masked by the frequent and continued use of drugs and food and it cannot be determined when pain would have spontaneously ceased. For example, when Banthine® bromide is used in the treatment of peptic ulcer, pain often is quickly re-

lieved and the patient may remain pain-free during months of Banthine therapy. However, when treatment with this drug is stopped, pain may rapidly recur and a follow-up x-ray examination show that the ulcer crater demonstrated at the onset of Banthine therapy remains unaltered. Symptomatic *relief* of pain by drugs or by food cannot be justly compared to *absence* of pain when no symptomatic treatment is administered. With this difference in mind it would appear that the high incidence of symptom relief which tends to develop rapidly in patients treated with vitamin U is a real and important indication that this form of treatment is effective in promoting the healing of peptic ulcers.

In considering normal standards of ulcer crater healing time, it must be stated that so far an insufficient number of detailed x-ray studies of large series of cases of peptic ulcer have been published. The control series of 68 cases used for a comparison with the present series of 54 cases (Chart 2) was published in 1946.[7] In the total series of 69 cases studied there were six cases of gastric ulcer with an average healing time of 42 days, and 63 cases of duodenal ulcer (one of these was omitted from the calculations because of a greatly prolonged healing time) with an average healing time of 37 days. Chart 2 clearly shows a greatly shortened healing time for the patients treated with vitamin U; and the rapidity of healing is emphasized when the average healing times of 14 days for gastric ulcer and 12.9 days for duodenal ulcer are compared with the 42 days and 37 days cited from the literature. In 1947 a large series of cases of benign gastric ulcer was reported with a healing time similar to that reported in 1946.[8] In a recently published report, ulcer crater healing time was completely studied in 31 cases of gastric ulcer,[9] and the time was shown to have varied between 2 and 15 weeks, with only eight cases in which there was complete healing in less than 4 weeks. The average healing time for the 31 cases was not stated, but from the data presented it can be calculated as 6.93 weeks. This healing time of slightly less than 7 weeks is comparable to that reported by Cummings and co-workers[7]—42 days (6 weeks).

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Hypothalamic Dysfunction

A Review of Experimental and Clinical Observation of Cardiac and Renal Aspects

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• *The nuclear cell masses of the hypothalamus act as autonomic regulators for visceromotor function. Through the correlation of impulses arising in or about the hypothalamus with the changes in cellular chemistry, there is provided, by mediation of the endocrines, a balanced control of water metabolism, renal function and cardiac action.*

Derangement of hypothalamic regulation causes specific clinical syndromes described by the general term "diencephalohypophyseal dystrophy." Cardiac abnormalities attributable to hypothalamic dysfunction include alterations in rate and various arrhythmias. Alteration in renal function includes hematuria, polyuria or relative anuria, and specific effects on electrolyte and nitrogen output.

THE HYPOTHALAMUS in man is about the size of the distal phalanx of the thumb—less than a cubic inch—yet without it man cannot exist, for it is essential in water metabolism, renal function, and cardiovascular dynamics. Lying between the cerebral peduncles, it includes the ventral walls and part of the lateral walls of the third ventricle and comprises the nethermost portion of the diencephalon. Within it are some fifteen nuclear cell masses, which, for purposes of convenience, may be classified into three groups: the anterior, in relation to the optic chiasm, the middle or tuberal nuclei above the hypophysis, and the posterior group which includes the mammillary bodies.

The middle group, which is the only one that changes much in evolution, is much less complex in adult humans than in mammals of the lower orders (or in human embryos), for in man the elementary instincts and vegetative needs are subordinate to the cortical development necessary for thought and special skills and movements. In adult humans there are two nuclei in the middle group,[19] whereas in rabbits, for instance, there are 30.

A beginning toward understanding of the role played by the hypothalamus in vegetative functions was made when Rokitansky[53] more than 100 years ago noted an association between hypothalamic damage and visceral changes. He observed a relationship between conditions affecting the base of the brain and gastric ulceration. At the turn of the century further clinical observations had to do with the development of Froelich's syndrome in persons with sleeping sickness.

In the first twenty years of this century, experiments with artificial stimulation somewhat like the diabetogenic third ventricle piqure done earlier by Claude Bernard were carried out. Karplus and Kreidl,[32-35] using electrical stimulation of the lateral hypothalamus, provoked changes in blood pressure and pulse rate, sweating, and pupillary dilation. Cushing removed the pituitary and noted that adiposogenitalism developed. Bard[1] related sham rage to the posterior hypothalamus, confirming that the hypothalamus is, among other things, a way-station for autonomic reactions accompanying the expression of emotions.

The results of early experiments with electrical stimulation were subject to criticism on the ground that the subjects had been anesthetized. More recently these objections were overcome by Hess[22] who, in a series of 3,500 experiments covering all diencephalic areas in 350 cats, used only light anesthesia when implanting the electrodes and rigidly fixing them to the skull, then waited until a half hour after the subjects had returned to consciousness before applying stimuli.

As to the clinical applicability of experimental data, as Brouwer[6] pointed out, experimental stimulation, being acute, brings into play accessory functional neuron chains. Clinical syndromes, on the other hand, are generally slow in evolution, and when a hypothalamic area is gradually destroyed, at least partial compensatory replacement of function may be expected on the part of the cortical vegetative centers and the medullary and inferior ganglionic reflex centers.[43] Thus the slowly developed clinical syndrome may not entirely match the phenomena swiftly induced by experimental stimulation.

The hypothalamus has been termed a "central

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ganglion" and, by Cushing and others, the cranial terminus of autonomic function. Both sympathetic and parasympathetic effects are mediated by hypothalamic nuclei. The posterior hypothalamus may be regarded, in this sense, as the rostral station for sympathetic or so-called thoracolumbar function, and the anterior hypothalamus as the station for parasympathetic, or craniosacral, integration. There are, however, cortical connections for some autonomic functions. As with sympathetic and parasympathetic fibers in end organs, the two areas work by reciprocal functioning. For example, the posterior hypothalamus has a vasoconstrictive function for conservation of heat, while the anterior portion promotes sweating and flushing to dissipate heat. The anterior hypothalamus initiates intestinal hypermotility and hyperphagia; the posterior, intestinal inhibition. Thus, the visceral effect of damage to the hypothalamus or of irritation of it by a lesion or toxin depends to some extent upon whether it is the anterior or the posterior portion that is involved.

The endocrines may be brought into action to a greater or lesser extent in hypothalamic phenomena. For example, hypermetabolism may be caused with or without thyroid participation.[7] Sex functioning is related particularly to the anterior hypothalamus, which has fibrous connection with the anterior pituitary. Upon this basis, Findley[12] theorized on a "stress" state of eosinophilism with secondary adrenal change. Endocrine participation appears to be much more important in water metabolism and renal function than in cardiac regulation.

RENAL ASPECTS

It is well established that the supraoptic and paraventricular nuclei of the anterior hypothalamus, the supraopticohypophyseal tract and the posterior hypophysis form a unit in the causation of diabetes insipidus.[13, 21] Verney[59] postulated that there are receptors in the supraoptic area that are responsive to osmotic changes in the blood stream. Spatz[54] and Hild[25] noted evidence that the neurosecretory ganglion cells of the preoptic and the other nuclei produce the antidiuretic hormone and that it is then transported along the connective tracts to the posterior pituitary for storage. Antidiuretic properties are present in extracts of both the hypothalamic and the hypophyseal elements of the unit, and injections of pituitrin or Pitressin® will compensate for diabetes insipidus caused by lesions in this unit. Diabetes insipidus may, however, occur as a result of lesions in the mammillo-infundibular nucleus alone, and in such instances the diuresis is not affected by injection of posterior pituitary extracts.[10, 42] In some cases diabetes did not develop even when the supraoptic nuclei were completely destroyed.[6]

In man, removal or destruction of the anterior hypophysis abates or prevents the diabetes insipidus that otherwise would result from injury to the neurohypophysis.[20] In experiments it has been observed that if an occluding clip is placed on the stalk of the neurohypophysis, diabetes insipidus results. Then if the anterior pituitary or the thyroid gland is removed, diabetes ceases; and if desiccated thyroid substance is given, it recurs.[41] From these observations it has been conjectured that the hypothalamus has a dual function in control of water balance by way of the endocrine system; that the neurohypophyseal system produces antidiuretic effect with thyrotropic hormone, and the anterior lobe produces diuretic effect with adrenocorticotropic hormone.[29] Thyroid substance is diuretic in action and the adrenal cortex may promote diuresis through its effect on the electrolytes of the blood stream.[48] A few nerve fibers enter the anterior lobe of the hypophysis, some from the posterior hypothalamus roundabout by way of the carotid plexus, and a few perhaps directly from the anterior hypothalamus. It has been reported that these nerve fibers influence the thyroid and the adrenal cortex by way of the chromophil cells of the anterior lobe. Heinbecker[23] observed that destruction of the supraoptic-paraventricular nuclei resulted in loss of the basophil cells of the anterior lobe, which gave rise to acidophilism and consequently to adrenocortical preponderance and hypothyroidism.

In studies recently carried out by the author in association with Goodman and Buschard[64] the renal function of patients undergoing routine ventriculography and encephalography was observed. The irritation of the central nervous system by the injected air caused not only protracted antidiuresis but also a reduction in the rate of electrolyte output. Thus, if posterior pituitary action alone were involved, these observations would be at variance with those of Starling and Verney[55] and of Van der Velden[57] who, in animals and man, determined that chloride output was not affected by giving pituitrin. In earlier experiments with animals, Weinberg and Marx[65] observed that denervation of the kidneys did not affect the antidiuresis or the lowered output of chloride and nitrogen that was brought about by the injection of an osmotic stimulus into the cerebral ventricular system, an observation that agrees, in this respect, with that of Starling and Verney. Perhaps it can be concluded that the neurohypophysis does not act alone in controlling electrolyte output by the kidneys and that other mechanisms contribute. Evidence of relationship of the hypothalamus to the kidney by the way of adrenocortical regulation of circulating electrolytes was summarized by Hume[27, 28] and Findley.[12]

Probably of greater significance in the work of the author and co-workers was the observation that great numbers of erythrocytes appeared in the urine during the height of the antidiuresis that occurred when air was injected into the nervous system. Evidence that a hypothalamic mechanism initiates renal glomerulitis and hematuria has been noted by other observers also: Brobeck and co-workers[4, 5] and Kennedy[36] reported similar observations in experimental studies on relationship of hypothalamic action to obesity. Renal vascular change after peripheral nerve stimulation was first studied by Goll in 1854.[17] Neurogenic renal cortical ischemia was observed in experiments by Trueta[56] and other investigators.[26] It was produced by stimulation of the hypothalamus anterior to the mammillary bodies. Similar ischemia with necrosis is sometimes observed clinically also.

The path from the hypothalamus to the kidney need not be direct. The author and co-workers noted hematuria upon stimulation of the hypothalamus even in animals with denervated kidneys. There is reason to believe that a hormone, either posterior pituitary or adrenal, is an indirect agent. (As yet there is no satisfactory delineation of the cause of nephrosclerosis or of some cases of glomerular nephritis.)

In considering the clinical syndromes that are generally regarded as etiologically related to hypothalamic dysfunction, it is of value to note that the presence (or absence) of diuresis is important in the differentiation of true anterior hypophyseal cachexia and Addison's disease from myxedema. Both hypophyseal cachexia and Addison's disease, like diabetes insipidus, are characterized by a delay in output of water that is ingested in large amount for test purposes, whereas in myxedema the diuresis is unimpaired. Normally, almost all of 1 liter of water should be excreted in three hours. Polyuria in adrenocorticalism derives from hypernatremia with secondary polydipsia rather than from action on the renal tubules as in diabetes insipidus.

It is assumed that there is in the nervous system an area, as yet not identified, that regulates circulating blood volume and shifts of fluid among the various organs and capillary beds. Undoubtedly such a mechanism, as well as the centrally initiated antidiuresis and electrolyte disturbance determined in observations previously mentioned,[64] plays a part in congestive heart failure. This aspect was discussed by Friedberg,[14] who concluded that the posterior pituitary antidiuretic hormone is not a primary factor in the edema of heart failure and that there is only suggestive evidence that the retention of sodium and water in adrenocortical syndromes is of significance in this clinical condition.

Diencephalic autonomic epilepsy may be accompanied by albuminuria and cylindruria.[11] Often this condition follows tumors or lytic lesions in the thalamus or, as in Penfield's early case, in the foramen of Monro, indicating remote activation of hypothalamic function. Cushing's hypothalamic syndrome and similar craniopathic conditions affecting metabolism cause no definite alteration in renal status except for diabetes insipidus in some cases. Most cases of diabetes insipidus occur secondary to tumors, Hand-Schuller-Christian disease, Boeck's sarcoid,[16] trauma,[8] syphilis, pellagra, or encephalitis.

CARDIAC ASPECTS

In addition to peripheral reflex and endocrine changes of hypothalamic origin that have indirect effect on the heart, the hypothalamus possesses a mechanism which directly affects the cardiac musculature.

The link between the brain—that is, emotions—and the heart has been observed for many centuries. William Harvey in 1628 stated: "A mental disturbance provoking pain, excess of joy, hope or anxiety extends to the heart where it affects its temper and rate." In 1747 the French cardiologist Senac made what was perhaps the first observation of the use of the Peruvian cinchona bark in clinical tachycardia, yet from that time to this century clinicians tended to regard arrhythmia as an intracardiac matter. In fact, hardly 100 years ago did Weber and Ludvig first describe the cardioinhibitory and cardioaccelerator nerves. Wenckebach, as recently as the First World War, in commenting upon the observation of extrasystoles in an Austrian army officer, called attention to the relationship between that condition and emotion. Numerous psychogenic and central nervous system disorders were listed by Orgain, Wolf and White[46] as causes of arrhythmia.

In 1875 Shiff and Danilewsky[9] noted that tachycardia occurred when stimulus was applied to the frontal lobe of the brain. The previously mentioned work of Karplus and Kreidl followed in 1913, and at about the same time Levy,[38] carrying out experiments that were prompted by the death of obstetrical patients from heart failure while in anesthesia, produced extrasystoles and paroxysmal ventricular tachycardia by stimulation of the cardiac sympathetic nerves in lightly anesthetized cats. In 1930 Beattie, Brow and Long[3] identified the principal anatomic nervous pathway concerned with this arrhythmic manifestation. This path is similar if not identical to the path traced by Karplus and Kreidl in the early part of this century as the route of sympathetic pressor and other effects originating in the hypothalamic nuclei (sweating, changes in heart rate, defecation, salivation, pupillary dilation, contraction of the bladder, elevation of blood pressure).

It extends by way of the periventricular system from the posterior hypothalamic nuclei down the medial longitudinal bundle, through the medulla, down the spinal cord to the thoracic sympathetic chain and so to the cardiac nerves. In the periventricular system, relationships are established with the motor cranial nerves for visceromotor function. Beattie, Brow and Long observed that the paroxysmal ventricular extrasystoles induced by posterior hypothalamic stimulation ceased when the medial longitudinal bundle adjacent to the aqueduct of Sylvius was sectioned, or when the stellate ganglion was removed, or when the preganglionic cardiac nerves were sectioned.

The early work of Karplus and Kreidl, who stimulated electrically the lateral wall of the third ventricle, and especially the posterior hypothalamus, lacked precision in comparison with the work of Hess, who pinpointed numerous areas with regard to the relationship of each to pulse rate and blood pressure. Hess noted in experiments that stimulation in the anterior tuberal area caused a decrease in blood pressure and that stimulation in the posterior tuberal area and in the posterior hypothalamus resulted in an increase. When stimulation was applied laterally, changes in heart rate as well as in blood pressure occurred. Stimulation of the lateral preoptic and lateral anterior hypothalamic areas caused a decrease in blood pressure and a slowing of the heart rate. When stimulation was applied in the posterior hypothalamus and at the posterior commissure and entrance to the aqueduct of Sylvius, tachycardia accompanied the pressor effect evoked. White,[66] during ventriculostomy on five conscious humans, stimulated electrically the posterior hypothalamus and observed that tachycardia resulted. Slowing of the heart rate followed stimulation of the medial preoptic area.

By injecting simple alkaloidal and osmotic stimuli into the third cerebral ventricle as a means of exciting the hypothalamus, the various auricular, nodal and ventricular cardiac irregularities were produced.[37, 63] A characteristic electrocardiographic pattern was consistently associated with each injected agent. The phenomena observed could have been produced only by way of both the cardioaccelerator and the cardioinhibitor paths—fibers from both the vagus and the sympathetic trunks extending as far as the ventricular musculature, largely by way of the intracardiac blood vessels.[67, 68]

It is not possible in every instance to determine the extent to which the hypothalamus participates in arrhythmia that is psychogenic or neurogenic. The medulla alone can maintain physiological cardiac action;[2] in fact, the cortex, hypothalamus, medulla, aortic and carotid sinus buffers, sympathetic ganglia and sinoauricular and auriculoventricular nodes all contribute to normal cardioregulation. The nerve pathway carrying the dominant regulatory impulse in any given case may be either above or below the hypothalamus. For example, heart block may change in degree upon inspiration by the patient, or coupled rhythm may follow emotional upset. All the various kinds of arrhythmia have been observed in connection with electric shock applied to the central nervous system in psychiatric treatment.[62]

Other evidence with regard to the role of the hypothalamus in cardioregulation has been noted in observation of patients with traumatic, febrile, and neoplastic lesions in or near the hypothalamus. In a case reported by Lucke,[39] ventricular extrasystoles were associated with a variant of diabetes insipidus. In Penfield's well known case of autonomic diencephalic epilepsy[47] owing to a ball-valve tumor in the foramen of Monro, the autonomic attacks were accompanied by tachycardia and bradycardia. Auricular flutter was associated with the presence of Boeck's sarcoid about the hypothalamus in a case reported by Gjersoe and Kyersulf-Jensen.[16]

Clinical syndromes deriving from hypothalamic dysfunction[10, 18] generally are adequately characterized by the term *diencephalohypophyseal dystrophy*.[31] They include complexes marked by hyper- or hypometabolism, duodenal ulcer, diminished libido, change in skin pigmentation, sleepiness, obesity, and cardiorenal abnormalities. Specific conditions of this kind are Froelich's adiposogenital syndrome, metabolic craniopathy, fibrous dysplasia of bone, nanism, Cushing's syndrome, and functional hypophyseal cachexia. Cardiac or renal manifestations of hypothalamic dysfunction are of clinical importance chiefly in diabetes insipidus, in the hypothalamic variety of Cushing's syndrome, in the previously mentioned organic hypothalamic arrhythmias, in congestive heart failure, and possibly in cases of hyperthyroid auricular fibrillation. In those conditions, treatment might be directed to the hypothalamus as well as to the heart or the kidneys.

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SAMA Honorary Memberships Open To Physicians

"KEEP UP with the young men who are keeping up with you" is the theme of a fall campaign now under way by the Student American Medical Association to encourage physicians to join the organization as honorary members. This new membership category was created at the request of doctors who wish to keep in touch with the student side of medical education, David Buchanan, national president of SAMA, said.

Honorary membership, with yearly dues of five dollars, entitles the physician to a subscription to the monthly 72-page Journal of the SAMA as well as participation in the annual convention and other activities of the association. Physicians and friends of the medical student interested in becoming honorary members should contact Mr. David Buchanan, Student American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

—*A.M.A. News Notes*

Retrolental Fibroplasia

Blindness in Infants of Low Weight at Birth

ALFRED APPELBAUM, M.D., *Huntington Park*

• *Retrolental fibroplasia is today the principal cause of blindness in children of preschool age, exceeding all other causes combined. The disease occurs in infants of low weight at birth, commonly those born prematurely. The incidence of the disease is rising at an alarming rate. Vitamin E deficiency, corticotropin (ACTH) deficiency, the use of cow's milk in place of mother's milk, and improper oxygenation have been suggested as etiologic factors but the cause remains a mystery. Often the incidence is high in institutions in which maximal care is given premature infants.*

Clinically, the disease advances through an "active" phase during which regression is possible, and a "subsiding" or "cicatricial" phase which terminates with the formation of a disorganized opaque mass behind the lens. The earliest manifestations are noted in the fundi. Hemorrhages, neovascularization, transudation commencing in the periphery, and retinal separation contribute to the formation of the characteristic retrolental membrane. The diagnosis may be made when the retrolental membrane is observed in the eye of an infant whose weight at birth was low. Differential diagnosis is required occasionally.

Thus far, no form of therapy has prevented or reversed the pathologic changes successfully. Use of vitamin E, corticotropin and mother's milk has not influenced the incidence of the disease. Avoidance of premature delivery if possible is indicated.

THE YEAR 1942 is of special interest in medical history as well as in world history. In that eventful year when the blackout and dimout entered our daily lives, Terry[26] described and named retrolental fibroplasia—a disease destined to bring a more genuine blackout or dimout into the lives of a segment of our population yet unborn. He stressed the novel association of the condition with prematurity. What may have appeared then as a clinical curiosity is recognized today as the principal cause of blindness in infants and children of preschool age, exceeding all other causes combined.

Travers[27] in 1820 gave the earliest description of a condition resembling retrolental fibroplasia. For some reason which cannot be explained, only isolated cases were reported before 1942. With gonorrheal ophthalmia controlled through legislation, congenital eye defects and the effects of injury had accounted for much of the visual impairment in infants and preschool children. Only a small percentage of preschool children were totally blind. Since 1942, retrolental fibroplasia has taken the lead with a steady and alarming increase in the number of cases. It now presents a problem which extends its tentacles into many areas. This is indeed a matter of great concern.

This disease strikes only infants, particularly those born prematurely with low weight at birth. Both eyes are usually affected. The retina and vitreous body are primarily involved. It is a clinical entity distinct from any type of disease of the eye that may likewise produce an end picture of disorganization of the retina and vitreous body. From the histopathologic standpoint, the name may not be entirely proper. However, from the purely clinical viewpoint, it serves adequately to describe the principal manifestation—the development of a fibrous membrane behind the lens.

The incidence of retrolental fibroplasia is peculiar in its manifestations. It is unknown for the country as a whole and varies considerably in different localities. In one hospital of an area only a few cases are seen; in another, in the same area, many cases. In the same institution, one year a high percentage of premature infants have the disease and the next year it becomes a rarity, although no material change in the care of the infants is made.

Premature infants weighing 3 pounds or less at birth and of gestational age six to seven months are the most frequent victims. Occasionally, it occurs in infants weighing more than four pounds at birth and in full-term infants. Owens[16] has not observed the development of retrolental fibroplasia in full-term infants.

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Although it is predominantly an American disease, cases have been reported in Canada, Denmark, England, France, Spain, Sweden, and Holland. Ryan[22] recently reported the first 23 cases in Australia. Boys are slightly more frequently afflicted than girls. In Gilger's[8] series, only boys were afflicted. Oddly, it occurs more frequently in infants born in hospitals — especially those of our larger medical centers—where such infants receive the best adjuvant care. In contrast, in a review of records for a two-year period (1947 and 1948), Exline and Harrington[6] could not find a single case among 80 infants who weighed less than 1,500 gm. (3 pounds 5 ounces) at birth, in the Charity Hospital of Louisiana at New Orleans, where maternal diseases, dietary privation and inadequate prenatal care are the rule.

Generally speaking, the lower the birth weight and the greater the prematurity, the greater the incidence. In multiple births, the lighter and weaker infant is more liable to have the disease. Although both eyes are commonly affected, one eye may occasionally escape with less damage and retain limited vision. Reports from different parts of the country indicate that the incidence of retrolental fibroplasia in infants weighing four pounds or less at birth ranged from zero to 32 per cent. The 32 per cent incidence was reported from a single hospital in Wilmington, Delaware, for a two-year period (1947-1949) by Lamotte.[12]

In California there are nearly 500 blind children of preschool age. Of these, 59 per cent are blind from retrolental fibroplasia.[3] The percentage may be even greater, if we take into consideration cases which have not yet been brought to the attention of schools for the blind.

The increasing incidence cannot be attributed to improper diagnosis or failure of recognition in the past. In certain localities the number of cases of retrolental fibroplasia far exceeds the number of cases of blindness that occurred prior to 1942 which could possibly be attributed to retrolental fibroplasia. Furthermore, it is not due to the increased survival rate. Statistics of many hospitals indicate that any increased survival rate is small compared with the apparent increase in the incidence of retrolental fibroplasia.

The author has recently concluded a study of the incidence of retrolental fibroplasia among prematurely born infants in the nursery of St. Francis Hospital, Lynwood. A total of 32 infants were observed. Four died early in life and the 28 survivors were followed through for a minimum of six months. The number of infants weighing three pounds or less and those weighing over three pounds were equally divided; none weighed more than 4 pounds 12 ounces. Each infant received dl-alpha tocopherol acetate "prophylactically" from the first week of life. Retrolental fibroplasia did not develop in any of the infants who weighed more than three pounds; in the group weighing three pounds or less the incidence was 18 per cent.

During each of the years 1949 and 1950, approximately three and a half million live infants were born in the United States. According to Simpson and Geppert,[23] 1.4 per cent of the total number of infants born weigh under 1,500 gm. (approximately 3 pounds) and according to Fletcher[7] the average mortality rate for premature infants is 29 per cent. With these figures, and applying the incidence of 18 per cent as the likely incidence among survivors in the average community, it may be anticipated that one infant in every 559 born alive, regardless of weight, may be blinded by retrolental fibroplasia.

ETIOLOGY

We are still in the dark concerning factors which may be responsible for the rather sudden appearance of the disease, and its increasing incidence. Numerous ramifications have been explored relative to the parents, the pregnancy, the delivery, and the management of the premature infant during his early existence. The latter is particularly important. The incubator phase of his life is quite complex. His status—as an extra-uterine fetus—presents countless problems, any one or more of which may hold the key to the cause of retrolental fibroplasia.

Efforts thus far have been rewarded only to the extent that a number of factors have been determined not to influence the development of the disease. These are: age of father or mother; heredity; familial trait; racial classification; social status and mode of life of the family; time of conception; incidence of infectious diseases in the community; food consumed by the mother during pregnancy; common infectious diseases of the mother (poliomyelitis, virus pneumonia, influenza) during pregnancy; chronic illness (cardiovascular disease, diabetes, tuberculosis, syphilis) during pregnancy; uterine or gestational diseases; order of birth; cause of the premature onset of labor; induced or prolonged labor; exposure to light; Rh factor; and use of the water-miscible multiple vitamins.

There are manifestations of the disease which suggest it may originate prenatally, and other factors that indicate postnatal origin. There is evidence that fibroplasia may be a syndrome of which the ocular disease is merely a part. Premature infants require and receive special attention in the form of modified diet, supplementary drugs and vitamins, blood transfusions, etc., to compensate for their immaturity. The resultant metabolic imbalance may provide causative factors capable of initiating the pathologic pattern of retrolental fibroplasia.

Several theories relative to etiologic derivation have been offered during the past three years. These are worthy of mention:

1. *Vitamin E deficiency* (Owens and Owens[17]): The immature organism particularly is susceptible to vitamin E deficiency. Vitamin E appears to be an important essential in animal nutrition for the normal development of the immature organism. The premature infant suffers from defective fat metabolism and is deprived of fat-soluble vitamins in the low-fat diet. The use of vitamin A and iron for the anemia further decreases the little vitamin E available to the premature infant.

2. *Corticotropin (ACTH) deficiency* (Reese and Blodi[20]): During the last trimester of pregnancy, there is a state of hyperadrenalism caused probably by the formation of corticotropin and adrenal cortical steroids in the placenta. The prematurely born infant is obviously deprived of this maternal hormonal environment necessary for normal development.

It is known that induced hyperadrenalism inhibits the growth of mesenchymal cells and that cortisone specifically inhibits the growth of capillaries. The neovascularization features of retrolental fibroplasia—that is, dilatation of existing blood channels and their proliferation into the vitreous body—may thus be accounted for by the lack of corticotropin.

3. *The use of cow's milk* (Hepner[9]): The physiologic deficiencies of the very prematurely born infant include a limited ability of the kidneys to concentrate electrolytes, manufacture ammonia and excrete phosphates. Cow's milk, which has taken the place of mother's milk, especially in institutions, has three times the electrolyte content of human milk. Balance studies have proven that this concentration approaches the limit of capabilities of the kidney of the prematurely born infant, giving rise to circumstances (edema, capillary leakage, hemorrhage, etc.) conducive to the formation of retrolental fibroplasia.

4. *Anoxia* (Szewczyk[24]): The premature infant is oxygen-deficient. During a period when the incompletely developed retina (and other fetal tissues) utilizes oxygen at a rapid rate, there exists a state of subclinical anoxia. If the need for oxygen by the retina is met partially, the disease develops in its attenuated form; if met completely, the disease does not develop at all. The oxygen tension in the blood is the important factor.

Factors which may predispose a premature infant to anoxia are given by Rudolph and Sirlin[21]:

(a) Premature disruption of the maternal circulation from any cause.

(b) Inability of the fetal circulatory system to carry on normally its physiologic functions because of immature development.

(c) Anemia of prematurity which is more severe than in full-term infants.

(d) Incomplete saturation of existing hemoglobin from immaturely developed lungs and respiratory controls.

(e) Pressure on the soft, malleable head against the pelvic floor during the second stage of labor.

(f) Oversedation and deep anesthesia.

(g) Position of baby sleeping face down on the mattress.

(h) Division of the maternal circulation between the fetuses in multiple births.

(i) Vaginal bleeding which occurs in a large percentage of mothers giving birth to children in whom retrolental fibroplasia develops.

(j) Poor circulation of air in bassinets.

(k) Acceleration of body metabolism by warm temperatures in the nurseries, so that even though the oxygen ratio of the environmental air be increased, it may not be sufficient to meet the requirements.

(l) Greater requirement of oxygen by the nervous system and retina.

Ingalls[11] proved by animal experimentation that anoxia is a teratogenic agent. A variety of defects of the eyes have been produced in both dead and surviving animals under conditions of anoxia—for example, retinal folding, coloboma and eversion of the retina, absence of the anterior chamber, and proliferation of vasoformative tissue. The kind of defect appears to be determined by the stage of gestation when the anoxia prevailed and by the degree of anoxia. This lends support to Szewczyk's theory.

5. *Hyperoxia* (Campbell[1]): Premature infants who received oxygen freely, both prophylactically and during periods of cyanosis, developed retrolental fibroplasia in greater numbers (18.7 per cent) than those who received it moderately (7.1 per cent). Ryan,[22] in support of the work of Campbell, advanced the idea that retrolental fibroplasia is due to the toxic effect of oxygen and that excessive oxygen treatment causes "the stimulation of mitoses and overgrowth of connective tissue, increase of vascularity, and increased growth rate of the inner layer of the optic cup leading to further detachment."

CLINICAL COURSE

Clinically, retrolental fibroplasia follows a fairly uniform sequence. At birth the eyes are typically normal for a prematurely born infant. During the first few weeks of life, the eyes of infants destined to have the disease do not differ from the eyes of infants in whom it does not develop. The usual degree of responsiveness may be noted during the brief intervals the eyes are opened, principally in the form of dislike for bright light. Occasionally, there is a

haze in the vitreous body or minor opacities, which soon disappear. All visible remains of the hyaloid system usually disappear early in postnatal life.

The "active" phase often commences before the infant has attained sufficient weight to be discharged from the premature nursery. It may commence as early as three weeks after birth; usually four to six weeks after birth. The initial manifestations are observed in the fundi: the retinal arteries become tortuous, assuming hairpin curves, and the veins become dilated to two or three times normal caliber. At this stage, regression is possible and in 50 to 60 per cent of cases the eyes return to normal. In others, however, the disease progresses with a series of devastating events: hemorrhages, neovascularization over the surface of the retina and in the vitreous body, transudation commencing in the extreme periphery of the fundus, and retinal detachment. These changes occur during the second and third month of life. At this stage, spontaneous regression is rare. Reese and Blodi[20] expressed belief that neovascularization may be present even before it can be recognized clinically. Vascular dilatation and neovascularization have been noted in the iris, simultaneously; also, in the optic nerves and orbit.

The "subsiding" or cicatricial phase commences about the third or fourth month of life. There is organization and contracture with the formation of a cyclitic membrane. The detached retina is drawn into the contracting fibrous tissue which forms the disorganized opaque mass behind the lens — the characteristic retrolental membrane. Commonly, this obstructs the entire pupil and the fundus reflex is no longer visible. The ciliary body is abnormally serrated. In the extreme periphery, tooth-like projections, often attached to uveal tissue, may be noted. The anterior chamber is shallow, often completely obliterated, with iris and lens in close proximity to the cornea. Glaucoma may ensue. Enophthalmos frequently is present in the end stage, probably from contractures resulting from the orbital involvement by the angioplastic process. When the retrolental membrane is formed, the eye ceases to grow. This retards the growth of the bony orbit.

In support of the theory that retrolental fibroplasia may derive from subclinical anoxia, Szewczyk[24] correlated the clinical course of the disease with anoxia. When the oxygen tension in the blood falls below the requirements of the fetal retina, the retinal vessels dilate, then become tortuous and, at the same time, new channels develop. If the demands for oxygen are still not satisfied, edema in the least matured parts of the retina develops (peripheral gray-white areas). The vessel walls begin to suffer, especially at the venous side, because the retina utilizes all the available oxygen, and transudation and hemorrhages take place. The transudation accounts for the vitreous body opacities. The gradual progressive retinal edema plus transudation from the vessels causes the gradual separation of the retina. Then atrophy and fibrosis set in. Similar changes occur in the ciliary body and iris, and no doubt in the brain and other nervous tissues.

McFarland and co-workers[14] also emphasized the measurable increase in the size of the vessels, varying between 10 per cent and 20 per cent, more pronounced in the veins, with anoxia.

It has been estimated that the active phase of the disease develops in approximately 50 per cent of all infants who weigh less than three pounds at birth. In cases in which the disease does not progress to the formation of the retrolental mass, the amount of residual damage depends on the extent of irreversible changes present when regression commences. In some cases regression occurs when there is advanced myopia or formation of a partial retrolental membrane. A membrane thinned in spots, one which covers only a localized portion of the retrolental space, or one which is limited to the periphery of the anterior vitreous body at the equator of the lens, may admit some light. This accounts for the apparent perception of light, in some cases.

Birthmarks of the hemangioma type are an interesting coincidence. These are known to occur in 1 per cent or 2 per cent of full term infants and in approximately 15 per cent of prematurely born infants, with or without retrolental fibroplasia. Rambar[19] emphasized the greater incidence of skin hemangiomas in premature infants of low weight at birth.

Similarity between the pathologic development of retrolental fibroplasia and hemangiomas of the skin in premature infants was noted by Reese and Blodi.[20] Both conditions are characterized by the angiomatous process (predominantly in the vitreous body, in the case of retrolental fibroplasia) and histologically identical newly formed vascular channels; both undergo progressive and then regressive changes with a final stage of cicatrization—all during comparable periods of time; and both are of higher incidence in the lower birth weight groups.

At least 80 per cent of all hemangiomas appear between the first and sixth week of life. This may account for the discrepancies in the literature wherein the exact time of appearance is not specified. The hemangiomas are usually multiple and grow during the first six months. Then, regression commences and by the end of the first year they have usually disappeared.

HISTOPATHOLOGY

In examination of lesions in the early stages of the disease Reese and Blodi[20] noted angiomatous tissue extending from the retina into the vitreous body,

particularly in the periphery around the base of the vitreous body. This angioplastic process in the vitreous body is the outstanding and characteristic early feature. The retina does not participate in the acute phase except as a source of the newly formed vessels. Transudation, hemorrhage and organization follow.

The earliest lesions thus far observed microscopically by Owens and Friedenwald[18] were found in the nerve-fiber layer of the retina. Here are observed patches or areas of proliferating endothelium, surrounded by an increase in the number of glial cells. Then areas of edema and small hemorrhages in the retina were observed. The next change was rupture of the internal limiting membrane with proliferation of the endothelial cells into budding new vessels along the inner layer of the retina and into the vitreous body. It was noted that eventually this tissue, increasing in density and quantity, became part of the loops of the elevated retina which coalesced to form the fibrous disorganized mass of tissue of the end-stage.

In eleven cases of retrolental fibroplasia studied, Dixon and Paul[5] found the essential lesions to be separation of the pars optica retinae and pars ciliaris retinae with proliferation of the underlying pigment epithelium. In some of these cases there was subretinal hemorrhage. Retrolentally, in addition to separated retina, which had usually undergone gliosis, there were, in varying amounts, fibroblasts and thin-walled blood vessels contributed by the retina and layers of condensed vitreous body. Remnants of the hyaloid artery and tunica vasculosa lentis were not observed.

DIAGNOSIS

The external manifestations of retrolental fibroplasia are well defined. When a beam of light is directed through the pupil, passing through the clear transparent lens, an opaque, whitish or grayish mass —often vascularized—can be seen immediately behind the lens. This is fairly diagnostic, especially when observed in both eyes of an infant born prematurely and of low weight at birth. The presence of a shallow anterior chamber, an atrophic iris, synechia, and elongated ciliary processes at the extreme periphery (behind the iris) further support the diagnosis. If it is possible to visualize the fundi, such changes as retinal folds, retinal detachment, hemorrhages, macular degeneration, healed foci resembling chorioretinitis and atrophied optic discs may be observed.

Retrolental fibroplasia may be confused with five conditions requiring differentiation:

1. *Retinal dysplasia* also involves both eyes but is not related to prematurity. The eyes are usually microphthalmic with cataract and glaucoma often supervening. The eye changes are accompanied by anomalies of the brain, heart, vascular system or skeleton, one of which often causes early death. Histologically, the retina shows signs of dysplasia, usually with the formation of rosettes and detachment. The connective tissue behind the lens seems to be the persistent primary vitreous body.

2. *Persistent hyperplastic primary vitreous body* (tunica vasculosa lentis) is unilateral and occurs in full-term infants. The eye changes are not accompanied by anomalies elsewhere. The affected eye is often smaller. The retrolental membrane is thickest in the center and fades peripherally, where long ciliary processes may be seen. Cataract and glaucoma from lens swelling develop. A persistent hyaloid artery may be seen if ophthalmoscopic examination is possible.

3. *Retinoblastoma* usually involves one eye, at first, and occurs later in life. The affected eye is of normal size. The fundus presents a glistening grayish or yellowish nodular mass with newly formed vessels, hemorrhages and foci of degeneration on its surface. The familiar "cat's eye" reflex is then present. X-ray studies reveal granular deposits (calcium) in the tumor mass. The intraocular tension is likely to be increased as the mass becomes more space-consuming.

4. *Pseudoglioma* involves one eye and follows some acute infection. The affected eye is usually flushed and painful. Hypotony is commonly present.

5. *Cataract* may involve one or both eyes. With the exception of the "white" pupil, the affected eye may be normal in every respect. The opacification is observed immediately behind the pupillary margin and this is facilitated when the examination is made through a fully dilated pupil. Vascularization is absent.

TREATMENT

While knowledge of the onset, clinical course and pathologic features of retrolental fibroplasia has advanced considerably in recent years, no form of therapy has been successful in reversing the pathologic disorganization of the retina and vitreous body after an eye has become deeply involved in the active phase of the disease; nor has it been possible to give the infants any useful vision. Surgical procedures have been attempted. Portions of the retrolental membrane have been excised to clear the pupillary area and make available for vision any portion of retina that might not be detached. The membrane removed usually contained disorganized retina. Visual improvement was negligible, if any, and the

technique has been abandoned. Attempts to eliminate the theoretical basic etiologic factors have had little influence on the incidence of the disease.

Results from the use of dl-alpha tocopherol acetate prophylactically — which only two years ago appeared so promising—have not been consistently satisfactory. Owens[15] still recommends its use prophylactically but now believes only the severity of the disease may be influenced favorably.

The benefits from the use of corticotropin and cortisone have stirred little enthusiasm; nor is the use of those hormones without systemic hazards. Locke,[13] Cook,[2] Day[4] and others have reported deaths in infants following the use of corticotropin and cortisone in the treatment of retrolental fibroplasia. The susceptibility of infants to infection appears particularly to be increased.

The use of human milk in place of cow's milk does not eliminate retrolental fibroplasia. Recently, Hess and co-workers[10] made an analysis of 317 living premature infants whose weight at birth ranged between 605 and 1,260 gm. (under three pounds). Of the total, 187 were born since retrolental fibroplasia was brought to the attention of the medical profession. Although all were fed breast milk, the eye defects noted in the survey included 13 cases of retrolental fibroplasia, an incidence of 7 per cent. Then again, none of the 80 infants reported by Exline and Harrington[6] received breast milk, yet amongst them there was not a single case of retrolental fibroplasia.

Proper oxygenation is receiving much attention. Szewczyk[24, 25] recently treated nine patients with early retrolental fibroplasia (that is, vascular engorgement, tortuosity of vessels, hemorrhages, and early retinal detachments) by placing them in an atmosphere with a concentration of 60 per cent to 70 per cent oxygen. In all cases, there was dramatic improvement in a relatively short time. He noted that the disease began to develop rapidly in seven premature infants when they were removed from incubators (where oxygen concentration was 50 per cent or more) and placed in bassinettes in the nursery where oxygen concentration was 22 per cent. After 24 to 48 hours in all cases there was development of dilated retinal vessels; and, in three to four days, tortuosity, neovascularization, hemorrhages and progressive peripheral retinal separation developed in almost all cases. The condition was rapidly reversed when the infants were placed back in an atmosphere of 60 per cent concentration of oxygen. In all cases, there was dramatic improvement in 24 hours and almost complete regression within three or four days.

Further studies have led to more specific recommendations: that premature infants be given minimal amounts of oxygen—just sufficient to meet their needs; that excessive oxygen concentrations be avoided; and that "weaning" the infant from oxygen be gradual, for even a normal adult cannot withstand sudden transfer to an environment of lowered oxygen concentration without disturbance of the central nervous system. Whether or not this procedure will reduce the incidence of retrolental fibroplasia remains to be proven.

THE PROBLEM

With few exceptions, if the disease has progressed through its usual course and the retrolental membrane has developed, the net result is a blind infant. Once the diagnosis is established, there is the dual task of dealing with parental reactions and providing training, education, and guidance for the tiny victim.

Parental reactions differ, and in many instances the exact emotional response to the infant's blindness is not in evidence at once. Gradually, it moulds into that of acceptance, conflicting feelings of rejection and overprotection, or emotional inability to deal with the reality of blindness. Parental feelings of guilt and frustration complicate the situation.

It is generally believed that the most potent of all influences on social behavior is derived from the primary social experience with the mother. "Acceptance" is a requisite for the favorable adjustment of the blind infant. From the social worker's standpoint, Wilson[28] considers the blind child accepted when the mother is able to concentrate on the child himself and not on his blindness; when she does not dwell on how the blindness affects *her* but rather on how it affects the child and how she can help him meet it for *his own* life satisfaction; when she makes the child a part of the family group.

Every phase of the blind infant's life centers around proper adjustment. In California this has not escaped the attention of the State Department of Education. In 1950, a program was organized to be executed as a function of the California School for the Blind at Berkeley. Field workers now visit the home and not only assist the family in the adjustments to the blind infant but suggest and demonstrate methods and materials which facilitate his learning. He is instructed in everyday duties. Parents are encouraged to meet regularly to exchange ideas and experiences. It is definitely to the advantage of the blind child to have this assistance as soon as the diagnosis is established. Blind persons make a more favorable adjustment if their early life afforded them a sense of physical and emotional secur-

ity. The early months are important also in preparing for the needs which are to follow. Many blind children have been placed in regular nursery schools and kindergartens for sighted children on an experimental basis. Their progress has been found to be very satisfactory.

The combined efforts of obstetrician, pediatrician, ophthalmologist, pathologist, epidemiologist, statistician, social worker, and educator are required to cope with the problem of retrolental fibroplasia. For the obstetrician there is a particular assignment:

1. Make every effort to reduce the incidence of premature births. Reexamine the causes of premature labor; some of these may be preventable. Confronted with indications for inducing labor prematurely, weigh them cautiously against the prospects of a blind baby. Keep in mind the simple formula: fewer premature deliveries = fewer cases of retrolental fibroplasia.

2. Consider carefully the need for drugs, narcotics and anesthetics before or during delivery if they will depress respiration or interfere with oxygenation in the mother or child. Any technique likely to produce anoxia in the infant may be a threat to his sight.

3. Following delivery of an infant of low weight at birth, advise the parents of the incidence of retrolental fibroplasia among infants in similar birth weight groups. Parents have learned to regard the incubator as a life-giving device but are completely unaware of the probability that blindness may be a concomitant of survival.

4. Provide ophthalmologic care as well as pediatric care immediately after delivery of an infant of low weight at birth. Continuous observation by an ophthalmologist may furnish the guidance necessary for proper oxygenation. Should the disease develop, an ophthalmologist is better prepared to interpret its significance to the parents.

5. Report any unusual circumstances relative to the pregnancy, the delivery, the mother, or the immediate postnatal care of an infant in whom retrolental fibroplasia develops. Note and record the incidence in your practice, in your hospital, in your community, and the factors which you believe may account for it. A passive attitude is not justified.

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CASE REPORTS

- **Stevens-Johnson Syndrome Treated with Cortisone and ACTH**
- **Measles Myelitis: Report of a Case and a Review of Diagnostic and Therapeutic Factors in Measles Encephalomyelitis**
- **Unilateral Deafness from Pontine Lesion**

Stevens-Johnson Syndrome Treated with Cortisone and ACTH

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In 1922, Stevens and Johnson[6] described two cases of eruptive fever, associated with stomatitis and ophthalmia. The condition was so unusual that they considered the syndrome a new clinical entity. The cutaneous lesions were widespread dark red maculae that became brownish papules in a few days. The eruption covered almost the entire body with the exception of the scalp. The mouth and lips were inflamed, eroded, and crusted. When the condition subsided, residual hyperpigmentation was present, but no scars formed. Both patients had purulent conjunctivitis which in one case developed into panophthalmitis with total loss of sight, and in the other caused greatly diminished sight, owing to corneal scars.

Since that time many similar cases have been reported. In 1929[5] Rutherford described cutaneous lesions in two boys which resembled those reported by Stevens and Johnson. Ultimately in both cases the eyes had to be enucleated. Both the patients had high and continuous fever, which in one case was attributable to lobar pneumonia but in the other could be ascribed only to the skin eruptions. Wheeler[7] reported a case in 1930 in which purulent conjunctivitis and keratitis followed the cutaneous phase and caused perforation and blindness in both eyes. Hernandez, in 1935, reviewed nine cases and reported a tenth. Seven of the patients in the nine cases reviewed became totally blind owing to keratitis. Koke[4] in 1941 tabulated reports of eighteen cases, of varying intensity, in which chemotherapy was not used. Fourteen of the patients had severe impairment of sight.

Goldfarb,[3] in a review of reported cases, said that the most striking and serious feature of the syndrome is severe conjunctivitis with keratitis. He observed that the eruptions of the skin and mucous membranes subside in six to eight weeks and the corneal lesions are the only serious threat. Goldfarb tabulated data on 21 cases, in most of which sulfonamides were applied locally to the conjunctiva and were given systemically. Eight of the patients were classified as blind. In bacteriologic examination of material from the site of infection the only pathogenic organisms noted were staphylococcus aureus or albus.

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Essentially the Stevens-Johnson syndrome is a severe systemic disease that is manifest as erythema multiforme, particularly of the periorificial areas, with associated ophthalmia.

Duke-Elder classified the lesions of the eyes in this disease into three groups—catarrhal, purulent, and membraneous conjunctivitis. Purulent conjunctivitis may lead to perforation of the globe by a corneal ulcer, as it did in one of the original cases reported by Stevens and Johnson. The pseudomembraneous form, which is more common, also may cause permanent damage. A membraneous form of conjunctivitis and keratitis, associated with typical skin lesions, was reported by Fuchs[2] in 1876 and by Barkan[1] in 1913, or 45 years and 9 years, respectively, before the syndrome was recognized and described as a separate entity.

Following is a report of a case observed not long ago by the author.

CASE REPORT

An 18-year-old girl was first examined by a dermatologist on March 5, 1951, because of "sores" on the face and inflammation of the left eye which had developed suddenly a few days before. The patient said that the first eruption was at a "break in the skin" caused by the teeth of a boy with whom she had collided in a basketball game three days previously.

Upon examination several bullous lesions on both cheeks were noted. They varied from 0.5 to 2 cm. in diameter and were surrounded by a narrow zone of erythema. The content of the bullae was purulent. The conjunctiva of the left eye was edematous and the blood vessels were engorged.

A diagnosis of impetigo contagiosa was made. Terramycin ointment was prescribed and 40,000 units of procaine penicillin (Crysticillin® fortified) was administered intramuscularly.

Two days later the cutaneous lesions had increased in number and the conjunctivitis was more intense. In addition there was bilateral blepharitis with bullae on the lid margins. Ophthalmic terramycin solution was prescribed for instillation every two hours during the day and terramycin ophthalmic ointment for application at night. Chloramphenicol, 250 mg. four times a day, was given orally. When the patient was examined two days later, the blood vessels in the throat were engorged and lesions resembling those of aphthous stomatitis were scattered on the buccal mucous membrane. The bilateral conjunctivitis had become purulent. In addition acute bilateral keratitis closely resembling dendritic herpetic keratitis was present and there was intense photophobia. The ulcer was deeper and the lesions more

extensive in the left eye than in the right. There were no inflammatory changes in the genitoanal area. The temperature was 99.6° F. The dermatologist* then recognized that the disease was Stevens-Johnson syndrome and called the author into consultation. The patient was immediately hospitalized.

The night of admittance to hospital, March 9, 1951, the temperature rose to 100° F. The pulse rate varied between 80 and 100 per minute. A rise of temperature approaching 100° F. occurred every afternoon thereafter for six days.

Twenty per cent cortisone in benzalkonium chloride (Zepheran®) solution 1:10,000 was instilled in each eye every two hours, 10 mg. of corticotropin (ACTH) was injected intramuscularly every six hours, and Tyrothricin® eye drops were instilled. The salt content of the diet was restricted to 500 mg. In addition the patient received chloramphenicol, 750 mg. every six hours.

The patient remained quite cheerful. The chief complaints were of photophobia and poor sight. There was no change in body weight during the period of hospitalization. There was no clinical evidence of fluid retention, and no evidence of potassium deficiency. Within two days after therapy was started the facial lesions began to dry up and to subside slowly. No new lesions appeared. On March 12 the chloramphenicol dosage was reduced to 500 mg. every six hours. The next day it was decreased to 250 mg. every six hours, and the dosage of corticotropin was reduced to 10 mg. every eight hours.

The facial lesions subsided so well that on March 15 the administration of chloramphenicol was discontinued. Although the photophobia diminished, there was no improvement, objectively, in the keratitis. In fact deeper infiltration of the cornea developed in the left eye and there was no change in the shallow superficial defect which had an irregular outline like the lesions of dendritic keratitis. Infiltration of the deeper layers of the cornea did not occur in the right eye. On March 17 when the patient was discharged the cutaneous lesions were almost entirely cleared but there was residual keratitis in each cornea.

The patient was advised to continue to use cortisone eye drops and tyrothricin ointment every three hours and to apply hot compresses afterward. Sulfonamides were given orally and penicillin systemically. The pupils were kept dilated with atropine. Despite those procedures, keratitis continued in both eyes and iritis with precipitates developed in the left eye. On April 11, typhoid antigen H was injected intravenously to induce hyperpyrexia, and later two more injections were given. No improvement was noted in the corneal ulcers. For more radical fever therapy, 8 cc. of raw milk was injected intramuscularly into the right buttock on April 28. The temperature rose to 103° F. and photophobia diminished. Three days later 10 cc. of raw milk was injected, then, after a three-day interval, 12 cc. Two days after the last injection the temperature returned to normal and the precipitates in the anterior chamber of the left eye became smaller in size and number. After two days at normal levels, the temperature rose to 102° F. on May 9, and a dry, hacking cough developed. On May 12 the temperature was 104.8° F. and the cough persisted.

The patient was hospitalized again. She complained of discomfort in the upper left quadrant of the abdomen. Nausea and anorexia were present. Increased irritability was manifest. In addition to the lesions of the eyes pronounced erythema of the nasopharynx was noted but there were no circumscribed lesions. Upon palpation the spleen was observed to be enlarged and tender. Increased breath sounds but no rales were noted in auscultation of the chest. The temperature was 102° F. and the pulse rate 98 per minute. The hemoglobin content of the blood was 13.8 gm. per 100 cc. Erythrocytes numbered 4,450,000 per cu. mm. and leukocytes 11,800 with a cell differential of 2 per cent monocytes, 13 per cent lymphocytes, 30 per cent non-segmented cells, 52 per cent segmented, and 3 per cent metamyelocytes. The blood sedimentation rate was 27 mm. in 30 minutes and 28 mm. in one hour. The urine was clear, the specific gravity 1.010, the reaction acid. It contained sugar and a trace of albumin. In microscopic examination of the urine, fine granular casts and a few epithelial cells, leukocytes and mucous shreds were noted. No pathogenic organisms grew on a culture of the blood. In an x-ray film of the chest, increased peribronchial markings in both lower lung fields were noted and it was observed that the dome of the left diaphragm was roughened. There was no free fluid in either pleural cavity. The lung fields otherwise were clear and there was no consolidation.

One thousand cubic centimeters of 5 per cent glucose in normal saline solution was given intravenously. A sponge bath with alcohol caused no reduction of temperature. Two hours after admittance the patient was given 500 cc. of distilled water orally. Thirty minutes later, after Dramamine® had been administered for nausea, 1 gm. of chloramphenicol was given and the patient vomited shortly thereafter. Ten milligrams of corticotropin was injected intramuscularly. A half hour later the temperature was 105.4° F. and at the end of an hour it was 104°. Chloramphenicol, 500 mg., was given and an hour later the dose was repeated. Five and a half hours after the first 10 mg. dose of corticotropin, a second dose, of 20 mg., was given. The temperature declined to 99.8°, and four hours later was 99°. The pulse rate had decreased to the normal range four hours previously.

Corticotropin then was given on a schedule of 10 mg. four times a day. The temperature and the pulse rate remained normal, the enlargement and tenderness of the spleen abated, and coughing diminished. The patient complained of abdominal cramps for two days. Gradually the corneal ulcers became shallower and photophobia diminished.

The patient left the hospital six days after admittance and from then until the administration of corticotropin was discontinued a month later the dosage was gradually reduced and the interval between injections lengthened. For the first week after discharge from the hospital, 10 units of whole liver extract was given intramuscularly twice a day.

Two flare-ups of keratitis, manifest in the breaking down of the corneal epithelium over small areas of the corneal scar, occurred subsequently. On both occasions local applications of cortisone were used. During the second exacerbation triple typhoid injections were given with beneficial influence on the corneal defects. Eight months after the onset of the disease, however, there was still active keratitis of low grade in the right eye. Visual acuity was 20/30 in the right eye and 20/40 in the left.

DISCUSSION

The only other report on the use of corticotropin in the treatment of Stevens-Johnson disease was published by Yates[8] and associates in 1951. The patient, a six-year-old boy, completely recovered after 48 days in the hospital and treatment with corticotropin and antibiotics. In the present case the local effect of the ophthalmic solution of cortisone was striking only as far as the hyperemia and the photophobia were concerned.

The origination of the disease at the site of traumatic contact with the teeth of a playmate may be of significance.

*The author wishes to thank the dermatologist, Dr. Maximilian E. Obermeyer, clinical professor and chairman of the Department of Dermatology, School of Medicine, University of Southern California, for his contribution to this study.

SUMMARY

In a case of erythema multiforme exudativum, the first lesion was on the skin, then successively the mucous membranes of the nose, mouth, and pharynx, and the conjunctivae and cornea became involved. The case was complicated by pronounced bronchial involvement and high fever. The severity of the protean manifestations of the disease was greatly diminished within four hours after a small dose of corticotropin was given. The ophthalmic manifestations, which had improved very gradually before the pronounced elevation of temperature, diminished rapidly afterward although keratitis did not completely heal.

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Measles Myelitis: Report of a Case and a Review of Diagnostic and Therapeutic Factors in Measles Encephalomyelitis

H. B. TAYLOR, M.D., *Los Angeles*

IT IS GRADUALLY being recognized that measles encephalomyelitis is not a generally benign complication of measles but, rather, is usually attended by permanent sequelae of greater or less severity. Particularly, it is important that electroencephalographic study be carried out on all patients, and that psychometric and psychiatric evaluation be done, both at the time of the original illness and again at a later date. There are indications that as time passes the original neurologic signs may be replaced by impaired mentality and behavior disorders.

It is well recognized that transient symptoms suggestive of encephalitis may be brought about by quite non-specific changes such as hyperthermia; and, less certainly, that rather clear-cut encephalitis may be accompanied by a normal electroencephalogram. It is therefore incumbent upon physicians to make electroencephalographic studies in all cases in which encephalitis is suspected. But if the tracings are normal, the diagnosis can be supported only with the soundest of neuropsychiatric evidence.

REPORT OF A CASE

A white boy, seven and a half years of age, was admitted to the communicable disease unit of the Los Angeles County Hospital on Jan. 25, 1952, with measles and weakness of the legs. Nine days previously catarrhal symptoms had developed and three days later generalized morbiliform rash appeared. (Concomitantly, six playmates of the patient had measles.) Although improving clinically, the patient was given penicillin on the sixth and seventh days of the illness. On the eighth day fever returned and generalized weakness of both legs was noted.

When examined the patient was alert and cooperative and appeared to have no discomfort. The rectal temperature was 101.4° F., the pulse rate 108 per minute and respirations 20 per minute. On the skin was a resolving bronze morbiliform rash. There was no evidence of lymphadenopathy or of meningeal irritation. Tendon reflexes were equal and apparently normally active and the superficial skin reflexes were intact. There was pronounced weakness of both lower extremities, and the patient was unable to walk.

The hemoglobin content of the blood was 13 gm. per 100 cc. Leukocytes numbered 9,500 per cu. mm., with polymorphonuclear cells 65 per cent of the total. The spinal fluid pressure was normal and the fluid was clear and colorless. The result of a Pandy test was negative. Four drops of the fluid reduced 1 ml. of Benedict's solution. The chloride content was 784 mg. per 100 cc. There were 47 lymphocytes per cu. mm.

Symptomatic therapy was given and the patient rapidly and progressively improved. He became afebrile on the third hospital day. Weakness in the shoulders and thighs noted on the third day had cleared by the sixth day, but the patient then was observed to have hamstring stretch pain, slight stiffness in the back and neck, and right lumbar scoliosis upon standing. He had been unable to walk unaided since the fifth day. On the seventh day he was transferred to another hospital for convalescent physiotherapy.

DISCUSSION

Since poliomyelitis is endemic in the area, it must be recognized that the diagnosis of measles myelitis is presumptive. The time intervals, however, are classical; and, in the last analysis, a certain degree of presumption must be conceded in the diagnosis of most of the infectious encephalomyelitic diseases.

Of the usual diseases of childhood, measles is exceeded only by mumps in association with secondary involvement of the central nervous system. The frequency of measles encephalomyelitis in relation to measles has been variously reported as 1:1,000 to 1:1,300, and there is some indication that the incidence may be increasing.[5] It has been observed that the incidence of central nervous system involvement is relatively higher in epidemic years.

There is no unanimity regarding etiologic delineation of measles encephalomyelitis. Rivers[6] speculated that there is either a periodic change in the measles virus or that some environmental or genetic change in the host is responsible. Lucksch[5] expressed the belief that predisposition to nervous system disease is a factor. Inductive reasoning gives rise to consideration of four possibilities: that the measles virus may acquire neurotropic characteristics; that a latent resi-

dent virus that affects the nervous system may be activated by measles; that neurotoxins may be elaborated during measles; that the measles virus is a sensitizing agent and the nervous system disease an allergic reaction. At present, the enigma cannot be resolved, but measles virus has been isolated from the brain of a person who died of encephalomyelitis.[8]

Generally the complication appears from the fourth to the sixth day following the rash; but it may occur during the catarrhal phase and has been observed as late as the 21st day after onset of the disease. Nervous system complications may occur in persons of any age, although the highest incidence is in patients five to eight years of age. The symptoms are non-specific, consisting of (in various combinations) rise in temperature, headache, lethargy, stupor, convulsions, stiffness of the back or neck, muscular weakness, spasticity, urinary retention, and abnormal reflexes.[4]

The complication has been divided rather arbitrarily into several types depending upon the predominant symptoms: meningeal; encephalitic; bulbar; striatal, characterized by abnormality of muscle tonus and choreo-athetoid movements; myelitic, typified by abnormality of reflexes, changes in muscle tonus and, sometimes, sensory changes. For completeness a "mixed" type is included.

Results of examination of spinal fluid may be indicative, although not pathognomonic. Usually the pressure is elevated, the protein content normal or increased, and the sugar content normal. There may be no cells in the fluid or as many as 1,000 per cu. mm., usually lymphocytes. The usual range is from 50 to 200 cells. Although Litvak[4] expressed the opinion that there is no correlation between spinal fluid content and prognosis, Sawchuk and co-workers[7] in a report on a series of cases noted a relationship between low cell content and severity of disease: 75 per cent of the patients who died had fewer than 25 cells per cu. mm. in the spinal fluid.

An electroencephalogram may occasionally be normal in definite clinical encephalitis, but usually the tracing is characterized by sharp and slow (2 to 4 second) waves; and the degree of abnormality is increased by hyperventilation. Generally the degree of electroencephalographic abnormality is directly proportional to the severity of the disease.

The pathologic changes in the brain and spinal cord are non-specific. Usually there is congestion and edema of the brain with petechial hemorrhages and thrombosis of the smaller vessels. The most constant microscopic observation is perivascular demyelinization. Less frequently noted is perivascular infiltration with small round cells. There is also a glial reaction. Rarely, no pathologic changes are observed.

The acute phase of the disease usually lasts five to ten days. Mortality rates are variously reported at from 10 to 40 per cent. With more prolonged and more accurate follow-up observation, an increasing incidence of permanent sequelae is being noted. It is possible that fixed abnormalities occur in more than 65 per cent of cases, and consist particularly of mental changes.[4] Frequently observed sequelae are: impaired intelligence, irritability and instability of mood, sleep disturbance, narcolepsy, metabolic and endocrine disorders, cerebellar ataxia, paresis of varying degree and extent, and epileptiform convulsions.

Since the opportunity for objective evaluation is at best limited, the utmost circumspection must be used in studying the results of any form of therapy. Non-specific measures such as control of convulsions, fever, and muscle spasm are, of course, routine. Convalescent measles serum and gamma globulin have not been found to be of value. The results of dehydration therapy are not encouraging. Results of therapy with intravenous administration of typhoid vaccine have been reported only fair. More recently cortisone and corticotropin (ACTH) have offered some promise, but more thorough trial is necessary before conclusions are warranted.[1]

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Unilateral Deafness from Pontine Lesion

A Report of Two Cases

J. M. NIELSEN, M.D., and
J. S. BERRYMAN, M.D., *Los Angeles*

UNILATERAL DEAFNESS from an intrapontine lesion is so rare that students are taught not to consider it strongly as a probable occurrence. During the past year, however, the authors have observed two cases with symptoms indubitably pontine in origin. In both instances the lesions were vascular, with probable involvement of the internal auditory artery.

REPORT OF TWO CASES

CASE 1: A white meteorologist, 25 years of age, was admitted to the hospital Aug. 20, 1951 with complaint of severe ataxia of limbs and speech. The patient had never been ill until March 26, 1951. On that date he stumbled over a box and fell. (In view of subsequent developments it is a question whether he did not fall because of an acute lesion of the brain stem.) In the fall he did not strike his head or lose consciousness, yet he had a headache and ringing in the right ear that night. Next morning there was numbness in the right side of the face, and it gradually spread to include the entire right side of the body. Nausea developed and became severe but the patient did not vomit. On the fourth day dysarthria developed and the patient was unable to walk because of incoordination. On the fifth day vomiting began and as the patient was lethargic he was admitted to a hospital in Pasadena.

A report of the neurological examination carried out at the time was supplied to the authors. The blood pressure

From the Long Beach Veterans Administration Hospital.

Presented before the Section on Psychiatry and Neurology at the 81st Annual Session of the California Medical Association, Los Angeles, April 27-30, 1952.

was 170 mm. of mercury systolic and 100 mm. diastolic. While there was no weakness of the extremities there were universal ataxia and loss of sensory perception on the entire right side of the body and face. Paralysis in the area of distribution of the left sixth and seventh nerves and complete deafness in the left ear were noted. The masseter and temporal muscles on the left side were also weak. Dysphagia and dysarthria were present. Hoffman and Babinski signs were present bilaterally. The deep reflexes were normal on the right but were increased on the left side.

Leukocytes numbered 17,700 per cu. mm. of blood, and 95 per cent of them were polymorphonuclear cells. The spinal fluid was bloody, and the total protein content was 81 mg. per 100 cc.

The initial impression was medullary thrombosis, and heparin was given intravenously by the drip technique for 15 hours. The condition of the patient became worse and tracheotomy was performed. The patient lost consciousness and remained in coma for two weeks. During that time keratitis developed in the right eye and tarsorrhaphy was done.

On Aug. 20, 1951, when the patient was first observed by the authors he was alert and cooperative although still unable to stand because of gross ataxia, and his speech was what is commonly described as "cerebellar." There was pronounced irregularity of respiratory movements. Muscle tone and strength were normal despite the incoordination. The sense of smell, the visual fields, and the fundi of the eyes were normal. Although the pupils were somewhat dilated, they reacted normally to light, and convergence was normal. The right superior, medial rectus and inferior rectus muscles were weak. There were coarse nystagmoid movements on lateral and vertical gaze. Anesthesia of the right side of the face and paralysis of the muscles of mastication on the left were noted. Paralysis of the left side of the face and deafness in the left ear still were present but neither condition was absolute. Hemianalgesia and thermanesthesia on the right side were noted. The cerebellar signs of ataxia, asynergy, and dysmetria were greater on the right and truncal ataxia was present. Babinski's sign was evoked weakly on the right side. Superficial abdominal reflexes were absent on both sides.

No abnormalities were noted in examination of the blood, and the spinal fluid was clear. In an electroencephalogram "some generalized 5 per second activity" was noted and it was interpreted as "evidence of a subcortical lesion." The ataxia gradually diminished slightly, the dysarthria and dysphagia moderately. The patient was confined to a wheel chair for weeks.

The final diagnosis was acute thrombosis in the left mesencephalon and pons which became hemorrhagic when heparin was given, causing occlusion of the internal auditory artery.

CASE 2: A retired army man, 68 years of age, was admitted to the hospital on Aug. 8, 1950, because of vomiting of blood-tinged material. The patient had been admitted in 1945 for the same reason and at that time had vomited daily for two months and had lost 20 pounds in weight. In 1944 the patient had had numbness about the left corner of the mouth. Gradually the numbness spread to include the left cheek and the left side of the forehead. Deafness in the left ear and drooping of the left corner of the mouth developed concomitantly. Tinnitus was not present, however, and the patient noted vertigo and nausea only upon hyperextension of the neck to look overhead. The symptoms continued without change until 1949, when the patient noticed an unsteadiness of gait and deviation to the left. There were no headaches or convulsions at any time.

The patient appeared to be poorly nourished. The blood pressure was 140 mm. of mercury systolic and 90 mm. diastolic, and the pulse rate was 75 per minute. A right inguinal hernia was present and there was tenderness in the epigastrium.

The sense of smell was undiminished, and the visual fields and the fundi of the eyes were normal, although there were no physiological cups. The jaw deviated to the left on opening and there was weakness of lateral motion to the right (with weakness of the temporal and masseter muscles). The corneal reflex was diminished on the left and there was hypesthesia in the area of distribution of the left trigeminal nerve. The left external rectus muscle was weak, with consequent diplopia. The left corner of the mouth sagged unless voluntary movements were made. Hearing in the left ear was 55 decibels less than normal. The biceps, triceps, wrist, knee, and ankle reflexes were all normal and symmetrical, and pathological reflexes were absent. The gait was ataxic, with deviation to the left, but the direction of deviation varied with the position of the head. While motor strength was normal throughout, adiadokokinesis in the left hand was noted. Sensory perception was unimpaired. Results of vestibular tests were normal.

The blood and the urine were normal and results of tests of the blood and spinal fluid were negative for syphilis. There were no cells in the spinal fluid but the total protein content was 78 mg. per 100 cc.

Extensive roentgenographic examinations were made of the skull in both Towne and Stenvers positions, of the gastrointestinal tract, and of the chest, but the only pathologic conditions noted were calcification of the internal carotid artery and healed tuberculosis of the upper lobe of the right lung.

The patient remained in the hospital from August to January without major episode. Then a psychotic state developed, with disorientation, uncleanliness, agggressiveness, and amnesia for recent events; but there were no hallucinations or any delusions except those based on disorientation. Horizontal and vertical nystagmus developed concomitantly with the mental disturbance.

The diagnosis was cerebral arteriosclerosis with involvement of the pontine branches and left cerebellar twigs.

SUMMARY

Two cases of unilateral deafness from vascular lesion in the pons are reported.

727 West Seventh Street.

California MEDICINE

EDITORIAL

Cobalt Bombs

THERE HAS BEEN some discussion in the popular press in recent months of the possibilities of improved control of cancer by the use of large sources of radioactive cobalt. When such large sources are used, they require enclosure in a heavy tube or tank, sometimes called a "bomb" or "cannon."

The theoretical advantages of cobalt are that the metal is more readily available and less expensive than radium. Further, if the cost of the activating pile (perhaps $25 million) is not considered, radioactive cobalt should be less expensive than existing types of "x-ray bombs" or "cannons" (that is, of 1 or 2 thousand kilovolt apparatus). Some believe that the cobalt bomb will permit more accurate tumor dosage and more effective techniques than are possible with high voltage x-ray equipment. Finally, the commonly planned beam of the cobalt unit is an almost monochromatic one, with a mean energy of about 1.2 million electron volts.

Most of the above advantages are more theoretical than real. In actual fact, cobalt-60 is not, at present, readily available. Further, the small plaques or slugs of cobalt require many months' exposure at the Canadian atomic pile at Chalk River to become suitably radioactive without at the same time causing undue interference with the other work going on at that center. Theoretically, a source of radioactive cobalt amounting to 1,000 curies could be made in about one year at Chalk River, but in actual fact it has taken longer. Indeed, the pile had to be shut down for a certain period because of contamination difficulties. Finally, practicing radiologists have more difficulty at present in securing radioactive cobalt than they do in obtaining naturally radioactive radium or high-voltage x-ray apparatus.

Additional disadvantages to any *large* amounts of artificial or natural radioactive material set up for use in the form of bombs or cannons are the very heavy shielding required and the necessarily cumbersome nature of the unit. The walls of treatment rooms have to be enormously thick and the doors of vast weight.

One final problem involved in radioactive cobalt is the relatively short half life of this substance (approximately 5.3 years as compared with 1,750 years for radium). This means that while one might start with a 100 curie cobalt bomb, it would be down to an effectiveness of about 52 curies in five years. This would necessitate lengthening treatment times progressively during the life of the bomb. Some workers suggest that cesium-137, which has a half life of 33 years, would be the "most economical and desirable isotope for teletherapy" (Brucer). Unfortunately, no large source of that element has yet been made available for therapy.

It is important to remember that radiologists have been using rays of various energies in the treatment of cancer since 1895. Radium has been available since 1901. X-ray tubes producing rays with energies of a million volts and more have been in use

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since the early 1930's. The radiations coming from radioactive cobalt are of the same type as those coming from radium and x-ray tubes. To date no one has proved that there is any curative power in the gamma rays from radium that does not exist in x-rays, and there is no reason to expect that the gamma rays from cobalt will do anything more than the gamma rays from radium. However, for certain tumor sites there may be some technical advantages in using radioactive cobalt rather than radium or high-energy x-rays.

Treatment with cobalt bombs is *not* generally available in this country at present. However, treatment with other types of ray-emitting units, both radium and x-ray, is widely available. Further, radiotherapists with equipment adequate for treating the majority of cases of cancer are at hand in most large American communities today.

In summary, therefore, radioactive cobalt bombs for medical use are still very much in the experimental stage. The type of rays emitted by these bombs does not act on cancer cells in any manner significantly different from that of filtered rays obtained from other more available x-ray and radium sources. Therefore, at least for the present, physicians treating cancer by radiological methods will continue to place major dependence on properly calibrated x-ray and radium therapy apparatus.

LETTERS to the Editor . . .

July 11, 1952

REFERENCE is made to the article by Dr. Frank Hinman, Jr., which appeared in the January 1952 issue of CALIFORNIA MEDICINE.

On page 3 of this article, the following statement appears:

> "Aureomycin, chloramphenicol and Terramycin are similar in antibacterial and other properties. In fact, it may be that chloramphenicol (which has been synthesized) is merely an active portion of the large Terramycin molecule."

The very extensive studies which have been carried out by our chemists have shown that, chemically, Terramycin differs radically from chloramphenicol, nor is the chloramphenicol molecule a component part of the Terramycin molecule. Of particular importance is the fact that Terramycin does not contain a nitrobenzene radical.

We are taking the liberty of bringing these facts to your attention since we are certain that you would not wish to have erroneous information go uncorrected.

Sincerely yours,

W. ALAN WRIGHT, M.D.
Director of Medical Service,
Chas. Pfizer & Co., Inc.

• *Dr. Wright's letter was referred to Dr. Hinman, who replied:*

The detailed chemical pattern of Terramycin had not been published at the time the article was written, and it is now apparent that the two substances are structurally unrelated, especially by the absence of the nitrobenzine radical in Terramycin. This correction is timely since chloramphenicol has very recently received adverse publicity related to aplastic anemia.

FRANK HINMAN, JR., M.D.

California MEDICAL ASSOCIATION

NOTICES & REPORTS

Council Meeting Minutes

Tentative Draft: Minutes of the 395th Meeting of the Council, Los Angeles, September 6, 1952.

The meeting was called to order by Chairman Shipman in Conference Room 9 of the Biltmore Hotel, Los Angeles, at 9:30 a.m., Saturday, September 6, 1952.

Roll Call:

Present were President Alesen, President-Elect Green, Speaker Charnock, Vice-Speaker Bailey, Councilors West, Wheeler, Sampson, Morrison, Dau, Lum, Montgomery, Bostick, Pollock, Carey, Shipman, Varden and Heron, and Secretary Daniels. A quorum present and acting.

Absent for cause: Councilors Loos, Ray, Frees and Kirchner; Editor Wilbur.

Present by invitation during all or a part of the meeting were Messrs. Hunton, Thomas, Clancy, Pettis and Gillette of the C.M.A. staff; legal counsel Hassard; Mr. Ben Read of the Public Health League of California; Mr. William M. Bowman, Mr. K. L. Hamman, Drs. Donald Cass and Francis T. Hodges of California Physicians' Service; county society executive secretaries Bannister of Orange and Thompson of San Joaquin; Ned Burman of public relations counsel; committee chairmen Dr. Francis J. Cox, John R. Upton, Christopher Leggo, Henry A. Randel, John B. Hamilton and Lewis T. Bullock; Drs. Frank Tallman and G. H. Crawfis of the State Department of Mental Hygiene; Dr. Wilton L. Halverson of the State Department of Public Health; Drs. Samuel R. Sherman and Garnett Cheney of the San Francisco Medical Society; Dr. J. Norman O'Neill and Mr. Thomas Welch.

1. *Minutes for Approval:*

(a) On motion duly made and seconded, minutes of the 394th Council meeting, held June 21, 1952, were approved.

(b) On motion duly made and seconded, minutes of the 232nd Executive Committee meeting, held June 21, 1952, were approved.

(c) On motion duly made and seconded, minutes of the 233rd Executive Committee meeting, held August 10, 1952, were approved.

2. *Membership:*

(a) A report of membership as of August 30, 1952, was received and ordered filed.

(b) On motion duly made and seconded, 107 members whose 1952 dues had been received since June 21, 1952, were reinstated to membership.

(c) On motion duly made and seconded, Dr. Charles H. Peppers of Riverside County was elected to Retired Membership.

(d) On motion duly made and seconded in each instance, eight applicants were elected to Associate Membership. These were: Wm. Lee Anderson, Alameda-Contra Costa; F. E. Davis and Robert M. Taylor, Kern County; Stanley Coffey, Wm. Y. Hollingsworth, Napa County; John A. Barger, Orange County; Irvin I. Schatz and John Long Wilson, San Francisco County.

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(e) On motion duly made and seconded in each instance, seven applicants were voted a reduction of dues because of illness or postgraduate study.

3. *Financial:*

(a) A report of bank balances as of August 30, 1952, was received and ordered filed.

(b) Discussion was held on the request of a county society for reimbursement for costs incurred in collecting A.M.A. membership dues. On motion duly made and seconded, it was voted to table the request.

(c) Statements for legal services, amounting to $825 and $3,950.69 for litigation in San Diego and $750 for litigation in Los Angeles directed against the Association and two other defendants, were presented. On motion duly made and seconded, it was voted unanimously to approve payment of all three statements.

4. *Committee on Hospitals, Dispensaries and Clinics:*

Dr. John B. Hamilton, chairman of the Committee on Hospitals, Dispensaries and Clinics, presented Drs. Frank Tallman and G. H. Crawfis, medical director and assistant of the State Department of Mental Hygiene. Dr. Tallman, discussed the work of his department, reported that an estimated 84 to 86 per cent of patients in state hospitals could be returned to civilian life under adequate staff conditions and reported on a program to notify the family physician when a state hospital patient was to be returned to his home. He asked the cooperation of the Association in obtaining physicians at adequate compensation.

Dr. Hamilton reported for the committee, requesting approval of a proposed Department of Mental Hygiene ruling which would permit staff physicians to consult with local physicians but not establish private practices beyond their state duties. On motion duly made and seconded, this report was approved.

On motion duly made and seconded, it was voted to approve a suggestion that the chief of the Department of Mental Hygiene be required by law to possess a Doctor of Medicine degree.

5. *Committee on Industrial Accident Commission:*

Dr. Francis J. Cox, chairman of the Committee on Industrial Accident Commission, reported that the insurance carriers had offered a 10 per cent increase in the existing level of industrial fees. He presented a statement which reviewed the history of industrial fees since 1918 which he requested authority to use in publicizing the studies of his committee and in appearing before an interim committee of the State Senate.

INTERIM SESSION

C.M.A. HOUSE OF DELEGATES

December 6-7, 1952

San Francisco

On motion duly made and seconded, it was voted to decline the offer of a 10 per cent increase in industrial fees, as inadequate and inequitable under present economic conditions.

On motion duly made and seconded, Dr. Cox was given authority to use his prepared statement after editorial review.

On motion duly made and seconded, Dr. Cox was voted authority to appear before the Senate Interim Committee.

6. *California Physicians' Service:*

Dr. Francis T. Hodges, Secretary of the C.P.S., reported that as of July 31, 1952, C.P.S. had 689,762 beneficiary and 10,878 physician members. He also reported on the recommendations of the C.P.S. Study Committee which are under consideration or actually in practice by the C.P.S. Board of Trustees.

Mr. K. L. Hamman, treasurer of C.P.S., reported on the financial statement.

7. *San Francisco Medical Society:*

Dr. Samuel R. Sherman, representing the San Francisco Medical Society, reported on the consideration given a proposal of the San Francisco Labor Council that health centers be established for A. F. of L. union members and their families. The decision of the committee he heads calls for (1) free choice of physician in all health insurance plans, (2) active opposition to the proposed health centers, (3) sound actuarial principles in all programs, and (4) medical control of all such plans.

Dr. Garnett Cheney, representing the president of the San Francisco Medical Society, further reported on this proposal and on a suggested plan under which medical service can be delivered to wage earners under acceptable conditions. He also reported that efforts are being made to develop a new approach to the question of making up fee schedules.

8. *Committee on Rural Health:*

Dr. Henry Randel, chairman of the Committee on Rural Health, reported on preliminary meetings held with representatives of the Agricultural Extension Division of the University of California, the State Grange, the California Federation of Farm Bureaus and the State Parent-Teachers Association. He suggested that a statewide Health Council consisting of

two representatives of each of these organizations, plus two representatives of his committee, be established, and the Council approved this suggestion.

9. *Committee on Psychology:*

Dr. Lewis T. Bullock, chairman of the Committee on Psychology, detailed a proposed legislative bill developed by his committee and discussed the terms of the bill. On motion duly made and seconded, it was voted to refer this proposal to the Committee on Public Policy and Legislation and to suggest that a joint meeting of the two committees be arranged.

10. *State Department of Public Health:*

Dr. Wilton Halverson, State Director of Public Health, reported that about 1,200 polio cases have so far been reported, about half the seasonal total of the epidemic of 1950, and that a sharp rise in cases is now apparent, indicating the possibility of a later seasonal tapering off than is usual. On encephalitis, 150 cases were reported in July and 350 in August. New cases are now dropping. There have been 36 deaths to date. Dr. Halverson outlined the methods being used to combat this disease and reported on blood testing being done on unexplained fever cases in several areas.

11. *Committee on Industrial Health:*

Dr. Christopher Leggo, chairman of the Committee on Industrial Health, presented a set of suggested standards for industrial nursing prepared by his committee and another set prepared by the A.M.A. and other national organizations. On motion duly made and seconded, it was voted to accept his report, including the proposed standards.

12. *Blood Bank Commission:*

Dr. John R. Upton, chairman of the Blood Bank Commission, reported that some of the blood banks may require extensions on the repayment of loans by the Association. He also reported that the eleven banks in the system had produced 59,325 units for civilians and 118,387 for the armed forces in the first six months of 1952. Present capacity of these banks is about 120,000 civilian units per year, which could be augmented by about 430,000 additional units for national purposes without increases in personnel.

13. *Public Policy and Legislation:*

Mr. Read reported on the November elections and discussed some of the ballot proposals. On motion duly made and seconded, it was voted to oppose Proposition No. 11.

14. *Medical Services Commission:*

A proposed program of the Medical Services Commission, embodying seven points, was presented and on motion duly made and seconded, was approved.

On motion duly made and seconded, it was unanimously voted to appropriate $5,000 as initial funds for the commission and to notify the commission that the Association is prepared to offer all services of its facilities and personnel to the commission until such time as a definite program is outlined and approved.

Time and place of next meeting:

The time and place of the next meeting were left at the call of the chair.

SIDNEY J. SHIPMAN, M.D., *Chairman*
ALBERT C. DANIELS, M.D., *Secretary*

Proposed Constitutional Amendments

(Second Publication)

Following are the proposed amendments to the Constitution of the California Medical Association that were introduced at the 1952 Annual Session and were carried over for action at the Interim Session. Both have been referred to Reference Committee No. 4, which is to make its report upon them available to delegates at least 30 days before the opening of the 1952 Interim Session in San Francisco, December 6, 1952. California Medical Association members who wish to record opinions on any of the proposed amendments may send them to the chairman of Reference Committee No. 4, Arthur A. Kirchner, M.D., 2007 Wilshire Boulevard, Los Angeles.

Submitted by Lyle G. Craig for Reference Committee No. 3, Interim Session, December, 1951.

Resolved, That the Constitution of the California Medical Association be amended as follows:

That in Article IV, Section 1, the first sentence be amended by deleting the word "regular" and inserting in its stead the word "Annual," so that this first sentence shall read:

"At each Annual Session the House of Delegates shall, by a majority vote, fix the annual dues to be paid by members of the Association for the ensuing calendar year."

The remainder of Section 1 shall be unchanged.

* * *

Submitted by Lyle G. Craig for Reference Committee No. 3, Interim Session, December, 1951.

Resolved: That the Constitution of the California Medical Association be amended as follows:

That in Article IV, Section 5, the first sentence be amended by striking out the word "regular" and inserting in its stead the word "Annual," so that the first sentence shall read:

"At each Annual Session of the House of Delegates the Council shall submit to it an itemized budget stating the proposed expenditures of the Association for the ensuing year."

The remainder of Section 5 shall be unchanged.

CALIFORNIA MEDICAL ASSOCIATION

Annual Meeting

LOS ANGELES
May 24-27, 1953

Papers for Presentation

If you have a paper that you would like to have considered for presentation, it should be submitted to the appropriate section secretary (see list on this page) not later than November 15, 1952.

Scientific Exhibits

The space available for scientific exhibits is limited. If you would like to apply for space, please write immediately to the office of the California Medical Association, 450 Sutter Street, San Francisco 8, for application forms. To be given consideration by the Committee on Scientific Work, the forms, completely filled out, must be in the office of the California Medical Association not later than December 1, 1952. (No exhibit shown in 1952, and no individual who had an exhibit at the 1952 session, will be eligible until 1954.)

Motion Pictures

There will be facilities available for motion pictures. If you would like to exhibit, send your application to Dr. A. E. Smith, 1930 Wilshire Boulevard, Los Angeles. The deadline is December 1, 1952.

SECRETARIES OF SCIENTIFIC SECTIONS

Allergy . . . . . *Norman Shure*
6317 Wilshire Boulevard, Los Angeles 48

Anesthesiology . . . . . *Joseph H. Failing*
475 Buena Vista Street, San Marino 9

Dermatology and Syphilology . . . *Frances Keddie*
300 Homer Avenue, Palo Alto

Eye, Ear, Nose and Throat—

Eye . . . . . *Alfred R. Robbins*
1930 Wilshire Boulevard, Los Angeles 5

ENT . . . . . *Francis A. Sooy (Asst. Sec.)*
490 Post Street, San Francisco 2

General Medicine . . . . . *William D. Evans*
10655 Riverside Drive, North Hollywood

General Practice . . . . . *A. Bradford Carson*
1515 Fruitvale Avenue, Oakland 1

General Surgery . . . . . *Arthur C. Pattison*
960 East Green Street, Pasadena

Industrial Medicine and Surgery . *Dan Kilroy (Asst. Sec.)*
3300 Third Avenue, Sacramento

Obstetrics and Gynecology . . . *Harold K. Marshall*
229 North Central Avenue, Glendale 3

Pathology and Bacteriology . . . . *A. R. Camero*
679 South Westlake Avenue, Los Angeles 5

Pediatrics . . . . . *Clement J. Molony*
416 North Bedford Drive, Beverly Hills

Psychiatry and Neurology . . . . . *A. E. Bennett*
2000 Dwight Way, Berkeley 4

Public Health . . . . . *Charles E. Smith*
U. C. School of Public Health, Berkeley 4

Radiology . . . . . *Calvin L. Stewart*
2330 First Avenue, San Diego 1

Urology . . . . . *James A. May*
2001 Fourth Avenue, San Diego 1

In Memoriam

COLLISCHONN, PHILIP. Died in San Francisco, August 13, 1952, aged 84. Graduate of the University of California Medical School, Berkeley-San Francisco, 1891. Licensed in California in 1892. Dr. Collischonn was a retired member of the San Francisco Medical Society, and the California Medical Association.

✤

COWGILL, CHARLES H. Died in Lynwood, August 3, 1952, aged 68, of cerebral hemorrhage. Graduate of the Minneapolis College of Physicians and Surgeons, Minnesota, 1908. Licensed in California in 1916. Dr. Cowgill was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

CRUIKSHANK, GEORGE H. Died in San Diego, August 27, 1952, aged 81. Graduate of Long Island College of Medicine, Brooklyn, N. Y., 1899. Licensed in California in 1900. Dr. Cruikshank was a member of the San Diego County Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.

✤

HARRIS, SQUIRE O. Died in Bakersfield, January 20, 1952, aged 72, of carcinoma. Graduate of Creighton University School of Medicine, Omaha, Neb., 1910. Licensed in California in 1943. Dr. Harris was a member of the Kern County Medical Society, the California Medical Association, and the American Medical Association.

✤

NORTHROP, ROBERT S. Died in Eureka, July 28, 1952, aged 74, of injuries rceived in an automobile accident. Graduate of Stanford University School of Medicine, Stanford University-San Francisco, 1922. Licensed in California in 1922. Dr. Northrop was a member of the Napa County Medical Society, the California Medical Association, and the American Medical Association.

✤

ROOT, PETER N. Died in Bakersfield, March 11, 1952, aged 65, of arteriosclerosis. Graduate of the University of Oregon Medical School, Portland, 1924. Licensed in California in 1924. Dr. Root was a member of the Kern County Medical Society, the California Medical Association, and the American Medical Association.

✤

STRAHLMANN, LOUIS. Died in San Diego, May 12, 1952, aged 60, of coronary artery disease. Graduate of Harvard Medical School, Boston, 1917. Licensed in California in 1920. Dr. Strahlmann was a member of the San Diego County Medical Society, the California Medical Association, and the American Medical Association.

✤

WEHRLY, JOHN. Died in Santa Ana, August 14, 1952, aged 84. Graduate of Missouri Medical College, St. Louis, 1890. Licensed in California in 1901. Dr. Wehrly was a member of the Orange County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

✤

WITTEN, PAUL. Died in San Fernando, August 1, 1952, aged 43, after an emergency appendectomy. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in California in 1937. Dr. Witten was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

Q. & A. on C.P.S.

Question: **Does C.P.S. pay for plastic surgery?**

Answer: The general policy is that C.P.S. will be liable for plastic surgery if it is performed primarily to correct a functional disturbance, providing the condition is not excluded by the terms of the contract. For instance, in cases of cleft palates and harelips, even though surgery would be performed, C.P.S. would not assume liability since these are congenital malformations which are not a benefit of a C.P.S. contract.

Question: **In many cases C.P.S. physician members treat C.P.S. "under income ceiling" patients for accidental injuries. If the patient later collects damages, can the physician member bill for an additional amount?**

Answer: In accordance with the terms as set forth in the "subrogation clause" contained in all C.P.S. contracts, the attending physician is not obligated to accept the sum by C.P.S. as full and final payment if the member treated recovers damages from a third party or insurance carrier.

Question: **Is preoperative care, which might possibly include consultation or x-rays, a benefit of the C.P.S. surgical contract?**

Answer: No. The C.P.S. contract becomes effective at the time actual surgery is performed. For those C.P.S. members who have surgical coverage only, preoperative care is a personal responsibility.

Question: **Am I able as a private physician to join the Blue Shield Plan as a beneficiary member, and if this is possible may I purchase hospital coverage only?**

Answer: All physicians or members of their staff are eligible to joint C.P.S.-Blue Shield as beneficiary members; however, hospital-only coverage is not available. All C.P.S. contracts must include coverage for professional service, i.e., surgical, medical-care-while-hospitalized or two-visit-deductible.

Question: **Why is it necessary for anesthetists and surgical assistant to indicate the length of time of their actual services when billing C.P.S.?**

Answer: California Physicians' Service payments for anesthetists and surgical assistants are based on the length of time of their respective services. As an example, C.P.S. pays a surgical assistant at major operations twenty dollars for the first two hours. If the length of time is not indicated, it is necessary to return the billings to the C.P.S. doctor in order to properly determine the amount of C.P.S. liability.

Question: **At times patients advise that C.P.S. rejects requests for x-rays while they are hospitalized and it is my understanding that x-rays are a benefit of C.P.S. hospital contracts.**

Answer: X-rays that are incidental to the admitting diagnosis are a benefit of the C.P.S. contract; however, C.P.S. will not pay for x-rays that would ordinarily be done on an ambulatory basis. X-rays must be related to the condition requiring hospitalization to be payable by C.P.S.

Question: **Is it possible to obtain C.P.S. coverage, other than on a group basis, through a place of employment?**

Answer: Yes. Individual family plan coverage is now available if the interested person is under the age of sixty and if the subsequent requirements of membership application can be met. Once a person is enrolled in the individual plan he may receive full benefits, at a slight increase in his cost of dues, up through and including any age over sixty.

Question: **When a C.P.S. member leaves his place of employment and transfers to the direct payment program, where the two-visit-deductible coverage is no longer available, is the medical-care-while-hospitalized contract considered a new contract?**

Answer: If a member had two-visit-deductible coverage under his group contract and received maximum benefits under that contract for any condition, he would still be eligible for completely new benefits for the same condition if he should take out medical-care-while-hospitalized on the direct payment contract.

Question: **A doctor's receptionist asks the question, "If a member is admitted to a hospital prior to the effective date of membership, will C.P.S. assume liability for any portion of the services rendered during that period of hospitalization?"**

Answer: No. C.P.S. contracts exclude all professional services and hospital care rendered during the period of hospitalization immediately following such admission.

Question: **On what basis was I charged by the Veterans Administration for a prescription I wrote for my veteran patient?**

Answer: A veteran prescription blank obtained from your pharmacy contains the following certification: "I am authorized to treat and prescribe for the above-named Veterans Administration patient." The Veterans Administration will always pay the pharmacy for such a prescription written by you on the basis of this certification. If you have not been authorized to treat the veteran, be sure that you issue prescriptions to him on a prescription blank that does not contain a certification. This will insure the veteran's filling the prescription at his own expense and avoid any liability on your part because of payment by the Veterans Administration on the basis of your certification.

NEWS & NOTES

NATIONAL · STATE · COUNTY

FRESNO

The Central Valley Psychiatric Society was formed last month by physicians who are members of the American Psychiatric Association. Officers of the new organization are: Dr. Mark Zeifert of Fresno, president; Dr. Rudolph Toller of Stockton, vice-president; Dr. V. S. Briden of Fresno, secretary-treasurer.

Dr. Zeifert said that "it is hoped that this will be the first district branch of the American Psychiatric Association on the West Coast."

SAN FRANCISCO

A grant of $22,259 to Stanford University School of Medicine for continued support of **training in diagnosis and treatment of cancer** was announced recently by the U. S. Public Health Service. A grant of $25,000 for the same purpose was made to the College of Osteopathic Physicians and Surgeons, Los Angeles.

* * *

Dr. Norman N. Epstein of San Francisco was elected president of the Pacific Dermatologic Association at the recent annual meeting of the organization in San Francisco. Dr. Louis G. Jekel of Phoenix was elected vice-president, and Dr. Paul Williams of Seattle assistant secretary. Dr. Ervin Epstein of Oakland was reelected secretary-treasurer.

More than 180 dermatologists were present at the meeting. The 1953 meeting is to be held in Seattle in July.

* * *

Dr. Charles Huggins, director of the Ben May Laboratory for Cancer Research and professor of surgery at the University of Chicago, has been appointed **visiting professor of oncology** at the University of California School of Medicine, San Francisco, for 1952. He will participate in the teaching of undergraduate medical students, deliver four lectures, and engage in the general program of the school's Cancer Research Institute.

* * *

Dr. Ernest Jawetz, while in the British Isles on sabbatical leave from the University of California School of Medicine where he is associate professor of microbiology and lecturer in medicine and pediatrics, lectured at Oxford University, delivered an Almroth Wright lecture at St. Mary's Hospital at the invitation of Sir Alexander Fleming, and gave the Macarthur postgraduate lecture at the University of Edinburgh.

SAN JOAQUIN

The program for the remaining five of eight **postgraduate lectures** scheduled for 1952 by the Stockton Postgraduate Study Club follows:

October 16: The Problem of Benign Pancreatic Disease—Albert Snell, M.D., of the Palo Alto Clinic, Palo Alto.

October 23: The Acute Abdomen and Its Management—Roy Cohn, M.D., associate professor of surgery, Stanford School of Medicine, San Francisco.

October 30: Treatment of Common Communicable Diseases—Edward Shaw, M.D., clinical professor of pediatrics, University of California School of Medicine, San Francisco.

November 13: Recent Advances in the Treatment of Hypertension—Maurice Sokolow, M.D., associate professor of medicine, University of California School of Medicine, San Francisco.

November 27: The Problem of Alcoholism—Paul Gliebe, M.D., assistant professor of psychiatry, University of California School of Medicine, San Francisco.

STANISLAUS

Dr. E. G. Allen, a general practitioner in Patterson since 1923, was publicly honored there September 21 in a community-wide celebration of Dr. Allen Day sponsored by the local chamber of commerce to pay tribute to the physician's "many years of unselfish service to the community." A parade of "Dr. Allen's babies," some of the more than 2,000 he delivered in 29 years of practice, opened the celebration.

GENERAL

The Committee on Pesticides of the American Medical Association currently is undertaking a country-wide toxicological study of cases of **poisoning resulting from the use of insecticides,** rodenticides, fungicides, weed killers, fumigants, repellents and related types of chemicals used in agriculture and the home. This information will be used to expand its permanent file of such cases for use by physicians and allied medical personnel.

Since much of the committee's information on pesticide poisoning has been compiled from unpublished isolated cases which were brought to its attention, the committee is appealing to physicians to submit records on cases of nonfatal and fatal poisonings from pesticides. The committee pointed out that summary data on the pertinent facts of the poisonings and the circumstances of their occurrence would be sufficient in most instances.

* * *

Hypertension and arrhythmias will be the subjects of the Fourth Annual Symposium of the **Washington Heart Association** and the Washington State Department of Public Health which is to be held November 7-8 in Seattle. Guest speakers are Dr. Myron Prinzmetal of Los Angeles, Dr. Stanley E. Bradley of New York, Dr. Robert W. Wilkin of Boston and Dr. Eugene B. Ferris of Cincinnati. There will be no registration fee.

* * *

The American Geriatrics Society recently announced that effective with January 1953 it will publish its own official periodical, *The Journal of the American Geriatrics Society*. Dr. Willard Thompson, of Chicago, president of the Society, will edit the journal.

* * *

The American Urological Association is offering awards totalling $1,000 (first prize of $500, second prize of $300 and third prize $200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to men in training to become urologists.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Jefferson, St. Louis, Missouri, May 11-14, 1953.

Full particulars may be had from the executive secretary, William P. Didusch, 1120 North Charles Street, Baltimore, Maryland. Essays must be in his hands before January 15, 1953.

* * *

Volume I, Number 1, of a new monthly Journal entitled **Obstetrics and Gynecology**, sponsored by the American Academy of Obstetrics and Gynecology, will appear in January, 1953. It is believed to be the first new monthly periodical exclusively devoted to this field to be launched in over thirty years, according to an announcement by Dr. Carl P. Huber, president of the Academy. The new journal will publish original articles, reviews, clinical notes, editorials, and book reviews covering the entire range of clinical obstetrics and gynecology. Dr. Ralph A. Reis of Chicago is the editor, and associate editors are Doctors F. Bayard Carter, R. Gordon Douglas, Ludwig A. Emge, Arthur T. Hertig, S. Leon Israel, William F. Mengert, Norman F. Miller, and Herbert E. Schmitz.

Papers to be considered for publication should be addressed to the Editor, Dr. Ralph A. Reis, 104 South Michigan Avenue, Chicago 3, Illinois.

* * *

Reserve officers of the medical services of the Army, Navy, and Air Force will be given complete information on all new directives, including pending Congressional legislation, governing their commissions, active duty requirements and retirement benefits in one of the feature presentations of the 59th annual meeting of the Association of Military Surgeons which will be held at the Statler Hotel, Washington, D.C., November 17-19, under the presidency of Major General Harry G. Armstrong, Surgeon General of the Air Force. Point credits for retirement will be given all eligible reserve officers attending the scientific session, it was announced by the Association of Military Surgeons of the United States.

POSTGRADUATE EDUCATION NOTICES

UNIVERSITY OF CALIFORNIA AT LOS ANGELES SCHOOL OF MEDICINE

Obstetrics and Gynecology—Medical Library, fourth floor C wing, Wadsworth General Hospital, Veterans Administration Center, West Los Angeles.

Dates: November 12, 13, 14, 1952—9-12 a.m., 2-5 p.m.

Fee: $50.00.

PROGRAM

November 12: 9:00-10:30—Danger Signs in Obstetrics—Alexander Glyn-Davies, M.D., formerly associate professor of obstetrics and gynecology, University of Sheffield, England.

10:30-12:00—Diabetes and Pregnancy—Blake Watson, M.D., assistant clinical professor of obstetrics and gynecology, School of Medicine, University of California, Los Angeles.

2:00-3:30—Carcinoma of the Uterus—Daniel Morton, M.D.

3:30-5:00—Urinary Tract Complications in Obstetrics and Gynecology—Willard Goodwin, M.D., associate professor of surgery, School of Medicine, University of California, Los Angeles.

November 13: 9:00-10:30—Carcinoma of the Ovary—James Nolan, M.D.

10:30-12:00—The Induction of Labor—Earl King, M.D., assistant professor of obstetrics and gynecology, University of California Medical Center, San Francisco.

2:00-3:30—Present Status of Rh Incompatibility—Bruce Rolf, M.D.

3:30-5:00—Bleeding in the Third Trimester of Pregnancy—Earl King, M.D.

November 14: 9:00-10:30—Pre- and Post-Operative Care in Gynecology—Earl King, M.D.

10:30-12:00—Indications for Hysterectomy—James Doyle, M.D.

2:00-3:30—Cesarean Section—Earl King, M.D.

3:30-5:00—Vulval Fluorescence as a Diagnostic Tool—Sidney Margolese, M.D., instructor, department of medicine, University of Southern California School of Medicine.

5:00—Question Period—Drs. King, Davies, Doyle and Morton.

Hematology in General Practice—Wadsworth General Hospital, Room 113, Veterans Administration Center, West Los Angeles.

Dates: November 5-December 10, 1952. Wednesday afternoons 2-4 p.m.

Fee: $30.00.

PROGRAM

This course is designed to emphasize major aspects of hematology as encountered in clinical practice. It will be centered upon case material available at Wadsworth General Hospital and general discussion of diagnosis and management of specific hematologic problems: Diagnosis and Management of the Hemorrhagic Disorders; Diseases of the Spleen and the Medical Indications for Splenectomy; Hemolytic Anemias; Iron Deficiency Anemia and Iron Metabolism; Macrocytic Anemias; Diseases Involving Changes in the White Blood Cell Picture; the Leukemias; Lymphomas and Multiple Myeloma.

Instructional Staff: William N. Valentine, M.D., associate professor of medicine, School of Medicine, Los Angeles. William S. Adams, M.D., associate professor of medicine, School of Medicine, Los Angeles. Phillip Sturgeon, M.D., assistant professor of pediatrics, University of Southern California School of Medicine. Charles G. Craddock, Jr., M.D., assistant professor of medicine, University of California School of Medicine, Los Angeles.

Electrocardiography—Business Administration and Economics Building (BAE), Los Angeles Campus (Westwood), University of California at Los Angeles.

Dates: November 5-21, 1952, Wednesdays and Fridays, 7:30-9:30 p.m.

Fee: $20.00.

PROGRAM

November 5—Presentation of the dipole concept and Einthoven's theories. Discussion of methods for taking unipolar extremity and precordial leads. Mathematical relationship between unipolar extremity and standard leads. The specialized tissues of the heart, anatomy and physiology.

November 7—Axis deviation. Right and left ventricular enlargement. Deflections of abnormally small and of abnormally large amplitude.

November 12—Bundle branch block, standard and precordial leads.

November 14—The T deflection. Primary and secondary abnormalities of T. The ventricular gradient. Pulmonary embolism.

November 19—Angina pectoris, coronary occlusion, changes in standard and precordial leads.

November 21—Esophageal leads. Intracardiac leads. General discussion and questions.

Contact: Application or requests for information concerning this course should be made to: Thomas H. Sternberg, M.D., Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles 24, Calif.

COLLEGE OF MEDICAL EVANGELISTS

Part-time Refresher Courses 1952-1953

Anesthesiology (4 months). Full time. Vacancy occurs each two months. Facilities limited to two students. Tuition: $300.00. Dr. Forrest E. Leffingwell and associates.

Roentgenology (32 periods). Tuesdays: 8:00-9:00 a.m., September 30, 1952, through June 2, 1953. Tuition: $100.00. Dr. Walter L. Stilson and associates.

General and Surgical Pathology (190 hours). Tuesdays: 1:00-5:00 p.m. and Thursdays: 1:00-3:00 p.m., Sept. 30, 1952, through June 4, 1953. Tuition: $175.00. Dr. Albert E. Hirst, Jr., and associates.

General Medicine (12 periods). Tuesdays: 7:30-9:00 p.m., Sept. 30 through Dec. 16, 1952. Tuition: $50.00. Dr. James J. Short and associates.

Traumatic Surgery (22 periods). Tuesdays and Wednesdays: 8:00-9:30 p.m., Sept. 30 through Dec. 10, 1952. Tuition: $50.00. Dr. G. Mosser Taylor and associates.

Surgical Anatomy (66 periods). Dissection, Demonstration, and Lectures. Mondays and Wednesdays: 1:00-5:00 p.m., Sept. 29, 1952, through June 3, 1953. Tuition: $250.00. Drs. Jacob Janzen, Elton L. Morel, and associates.

Surgical Anatomy (34 periods). Demonstration and Lectures. Wednesdays: 3:00-5:00 p.m., Oct. 1, 1952, through June 3, 1953. Tuition: $100.00. Drs. Jacob Janzen, Elton L. Morel, and associates.

Physical Medicine (8 periods). Wednesdays: 8:00-9:00 a.m., Oct. 1 through Nov. 19, 1952. Tuition: $30.00. Dr. Fred B. Moor and associates.

Surgical Physiology (33 periods). Tuesdays: 9:00 a.m.-12 noon, Sept. 30, 1952, through June 2, 1953. Tuition: $75.00. Dr. Harry A. Davis.

General Management of Diabetes Mellitus (11 periods). Thursdays: 9:00-11:30 a.m., Los Angeles County General Hospital. Oct. 2 through Dec. 18, 1952. Tuition: $60.00. Dr. James J. Short.

Genito-Urinary Diseases. Daily: 10:00 a.m. to 2:00 p.m., Nov. 17 through 21, 1952. Tuition: $60.00. Classes are conducted at the Ambassador Hotel, Los Angeles, under the auspices of the Los Angeles Urological Society.

Surgical Diseases of the Peripheral Vascular System (8 periods). Tuesdays: 7:00-8:30 p.m., Jan. 6 through Feb. 24, 1953. Tuition: $30.00. Dr. Carl H. Talmadge and associates.

Differential Diagnosis of Internal Diseases (12 periods). Tuesdays: 8:00-9:30 p.m., Los Angeles County General Hospital. Jan. 6 through March 24, 1953. Tuition: $50.00. Dr. Julius Bauer.

Diseases of the Chest (2 days). Thursday and Friday, Los Angeles County Medical Association. Jan. 22 and 23, 1953. Tuition: $15.00. Lecturers to be announced.

Dermatology (12 periods). Wednesdays: 8:00-9:30 p.m., Jan. 7 through March 25, 1953. Tuition: $40.00. Dr. Clement E. Counter and associates.

General Urology (9 periods). Wednesdays: 8:00-9:30 p.m., Jan. 7 through March 4, 1953. Tuition: $35.00. Drs. Roger W. Barnes, R. Theodore Bergman, and associates.

Proctology (10 periods). Thursdays: 8:00-10:00 a.m., Jan. 8 through March 12, 1953. Tuition: $50.00. Dr. Malcolm R. Hill and associates.

Otolaryngology (8 periods). Tuesdays: 8:00-9:30 p.m., Feb. 10 through March 31, 1953. Tuition: $30.00. Dr. H. James Hara and associates.

Histology and Histopathology of the Eye (15 periods). Wednesdays: 7:30-9:30 p.m., Feb. 25 through June 3, 1953. Tuition: $60.00. Dr. I. G. Sommers.

Varicose Veins (6 periods). Tuesdays: 7:00-9:00 p.m., March 3 through April 21, 1953. Tuition: $25.00. Dr. Carl H. Talmadge and associates.

Gynecology (10 periods). Wednesdays: 8:00-9:00 a.m., March 25 through May 27, 1953. Tuition: $30.00. Dr. Dell H. Haughey and associates.

Operative Surgery (8 periods). Tuesdays: 7:00-9:00 p.m., April 7 through May 26, 1953. Tuition: $150.00. This course in operative surgery will be a combined lecture and laboratory course designed to provide opportunity for the student physician to personally perform standard major operations. Dr. Harry A. Davis.

Endocrinology (8 periods). Tuesdays: 8:00-9:30 p.m., Los Angeles County General Hospital. April 7 through May 26, 1953. Tuition: $30.00. Dr. Julius Bauer.

Thoracic Surgery (8 periods). Wednesdays: 8:00-9:30 p.m., April 15 through June 3, 1953. Tuition: $30.00. Dr. Lyman A. Brewer.

Minor Orthopedic Surgery (8 periods). Thursdays: 8:00-9:30 p.m., April 16 through June 4, 1953. Tuition: $30.00. Dr. Alonzo J. Neufeld.

Diseases and Injuries of Bones and Joints. Full time. July 6 through 31, 1953. Tuition: $100.00. Drs. G. Mosser Taylor, Alonzo J. Neufeld, and associates.

Contact: For further information, write Chairman, Section on Graduate and Postgraduate Medical Education, College of Medical Evangelists, 312 North Boyle Ave., Los Angeles 33, Calif.

INFORMATION

The Stanford Convalescent Home

IN RESPONSE to inquiries from physicians about the Stanford Convalescent Home the following information has been prepared:

Located near Palo Alto, Calif., on the Stanford University property, the Home is an entirely independent, non-profit institution established to provide convalescent care for children between the ages of four and twelve years. Patients are accepted from any physician, hospital or clinic in the Northern California area on approval of the medical director. The kinds of patients accepted include those with rheumatic fever, allergic disorders, convalescent poliomyelitis, recurrent or chronic respiratory infections, and especially simple malnutrition or debility in children from inadequate homes or who are convalescing from a recent acute illness. Patients with active tuberculosis are not accepted; but tuberculous children with healing of the primary complex and with negative gastric washings who are in need of convalescent care are taken on special approval of the medical director.

The Convalescent Home is supported in part by a number of public and private agencies and benefactors so that the charge per patient is adjusted according to the economic circumstances of the family and other factors. The range is from no charge to the full rate of $240 per month. Application may be made directly to the medical director, Dr. Harold K. Faber, at Stanford University Hospital, San Francisco, on the regular admission blank provided, or through the medical social worker, Miss Adele Moroney, at the admission office of the Home at 2412 Clay Street, San Francisco, phone WEst 1-7535.

The length of stay varies from a few weeks to many months, depending upon the nature of the illness and the progress of the particular child. Few patients remain longer than a year. Insofar as possible the visiting staff will carry out the treatments recommended by the referring physician. Special diets, including elimination diets for patients with allergic disease, are followed. Physiotherapy is available through the cooperation of the Stanford School of Physiotherapy. X-ray, laboratory work, and consultations in the medical specialties are available through local visiting and attending doctors and are used freely. Limited dental service is available.

Monthly progress reports to the referring physician keep him informed of the patient's condition while at the Home.

The Convalescent Home is part of the Palo Alto Unified School District so that the child's education can proceed in an uninterrupted fashion. A very active occupational therapy department is under the direction of a full-time therapist. Craftwork and other interesting work is provided for all children and is used as an adjuvant to medical therapy whenever possible. The home has its own Cub pack, Scout troop, Brownie group, etc. Parties and special events are held frequently.

Further information and application blanks may be obtained from the medical social worker at the admitting office of the home, 2412 Clay Street, San Francisco (phone WEst 1-7535), or from the superintendent, Mrs. Ruth Atwood, R.N., at the Stanford Convalescent Home, Stanford, Calif. (phone DAvenport 3-6158). Physicians or others interested in visiting the home are welcome at any time.

Warning Label on Chloromycetin

The Food and Drug Administration of the Federal Security Agency recently announced its decision to permit the continued distribution of the antibiotic drug Chloromycetin under revised labeling that will caution physicians explicitly against its indiscriminate use.

Charles W. Crawford, commissioner of food and drugs, said: "The Administration has weighed the value of the drug against its capabilities for causing harm and has decided that it should continue to be available for careful use by the medical profession in those serious and sometimes fatal diseases in which its use is necessary."

The commissioner said that "FDA's decision was similar in principle to one made every day by thousands of doctors throughout the country who weigh the need for a potent drug against the possibility of harm to the patient."

Reports of blood disorders attributed to Chloromycetin led to a nationwide survey by the FDA late in June of the case records in hospitals and clinics. The case histories turned up by this survey were referred to the National Research Council for its aid in evaluating the information. FDA's decision was based on the findings and recommendations of a special committee of the Research Council's Division of Medical Sciences.

The committee of outstanding authorities on hematology and infectious diseases was headed by Dr. John Holmes Dingle, professor of preventive medicine at Western Reserve University, Cleveland.

The committee considered the records of 410 cases of serious blood disorders, of which 177 were definitely known to have been associated with the use of Chloromycetin.

In 61 cases Chloromycetin was the only drug administered. In the remaining 116 cases other drugs had also been given. In both groups fatalities totaled 50 per cent, attributable to aplastic anemia and related conditions in which the bone marrow has lost its ability to manufacture both red and white cells of the blood.

A group of 168 cases, including 97 cases of aplastic anemia, was eliminated from consideration by the committee because it was determined that Chloromycetin had not been administered. A remaining group of 65 cases in which Chloromycetin may or may not be involved, continues under investigation.

It is estimated that since the drug came on the market in 1949, it has been administered to something like eight million patients.

The report of the special committee addressed to Dr. Irvin Kerlan, acting medical director of the FDA, by Dr. M. C. Winternitz, M.D., chairman of the National Research Council's Division of Medical Sciences, read as follows:

"In your letter of 23 July you requested that the National Research Council appoint a group to review and evaluate the information assembled by the Food and Drug Administration on the incidence of serious blood dyscrasias associated with the use of chloramphenicol.

"An *ad hoc* conference was held on 6 August and reviewed all available data presented by the Food and Drug Administration and by Parke, Davis and Company.

"The consensus of the conference was as follows:

"1. Certain cases of serious blood dyscrasias (aplastic anemia, thrombocytopenic purpura, granulocytopenia, and pancytopenia) have been associated with the administration of chloramphenicol.

"2. Although this complication has thus far been uncommon, it is sufficiently important to warrant a warning on the label of packages of the drug and in advertisements of the drug and the recommendation that chloramphenicol not be used indiscriminately or for minor infections.

"3. When prolonged or intermittent administration is required, adequate blood studies should be carried out.

"4. In view of the paucity of information at the present time the conference hopes that further study of serious reactions to chloramphenicol and other drugs will be promoted. The records of the Veterans Administration and military forces could be of great value in providing some of the desired information."

* * *

Chloromycetin is one of five antibiotic drugs which are certified by the Food and Drug Administration. Testing procedures, packaging and labeling are spelled out in detail in official regulations, and every batch manufactured is double checked in the FDA laboratories in Washington.

Commissioner Crawford said the labeling of Chloromycetin will be changed to include the following warning:

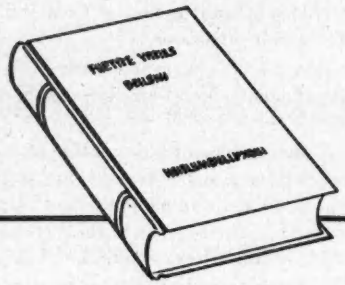
(TO APPEAR AT TOP OF CIRCULAR)

"Certain blood dyscrasias (aplastic anemia, thrombocytopenic purpura, granulocytopenia and pancytopenia) have been associated with the administration of Chloromycetin. It is essential that adequate blood studies be made when prolonged or intermittent administration of this drug is required. Chloromycetin should not be used indiscriminately or for minor infections."

(ON THE LABEL)

"WARNING: *Blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made."*

Dr. Kerlan, who is FDA's ranking medical officer, said that the recent experience with Chloromycetin "is an impressive reminder that highly potent drugs must be treated with extreme care and should not be employed unless there is a clear-cut indication that they are needed." He said there is no way of foreseeing as yet all possible reactions which may develop in patients after a drug becomes widely used.



THE PHYSICIAN'S *Bookshelf*

THE OCULOROTARY MUSCLES — Second Edition. Richard G. Scobee, B.A., M.D., F.A.C.S., Assistant Professor of Ophthalmology, Washington University School of Medicine, St. Louis. The C. V. Mosby Company, St. Louis, 1952. 512 pages, $11.00.

The first edition of this book appeared in 1947 and while there has been some controversy regarding some of the material it was very generally accepted and today is probably the most popular of all books on extraocular muscles and the one most widely used by residents in ophthalmology. The book was intended primarily for the student.

The second edition has been enlarged and certain changes have been made which improve the value of the book. Changes in terminology to conform with the generally accepted terms has removed some confusion that existed in the first edition. As stated in the preface, the author's discussion of the book with Dr. Walter Lancaster resulted in changing certain parts of the volume.

While the general format remains the same except for the color of the cover the number of pages has been increased from 359 to 512. The chapters dealing with physiology, retinal correspondence, the horopter, Sherrington's law, Listing's law, and some recent ideas on proprioception have been rewritten in more detail. Extension additions have been made in the chapters on hyperphoria and on exophoria. The addition of the section on intermittent exotropia to the chapter on exotropia has increased the value of that chapter a good deal. The section on heterotropia has been largely rewritten as has also the section dealing with the cover test. The final chapter on reasons for failure in tropia surgery is new and adds a good deal to the book. In addition to the above other portions of the book have been altered.

The addition of 47 new illustrations also enhances its teaching value. The index has also been enlarged.

One regrets that the references at the end of the chapters are not given in the usual detail.

This second edition is an even more outstanding contribution to ophthalmic literature than was the first edition.

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NORMAL BLOOD PRESSURE AND HYPERTENSION —New Definitions. Arthur M. Master, M.D., Cardiologist, Mount Sinai Hospital; Charles I. Garfield, M.D., Research Assistant in Cardiology, Mount Sinai Hospital; and Max B. Walters, M.D., F.R.C.P. (Can.), formerly Research Assistant in Cardiology, Mount Sinai Hospital. Lea and Febiger, Philadelphia, 1952. 144 pages, $4.00.

As indicated by the title of their monograph, the authors have attempted to define and to establish the normal range of blood pressure in the different age groups and in both sexes. The literature pertaining to the subject is reviewed adequately.

In utilizing the results of a statistical analysis of 74,000 unselected subjects, the authors propose new criteria for the normal range of blood pressure based on the age and the sex of the individual. The significance of these criteria in relation to coronary artery disease, myocardial infarction, and cardiac enlargement is discussed.

The outstanding features of this monograph are its excellent bibliography and the plea of the authors for the physician to disregard the height of the blood pressure reading and concentrate on the clinical findings. This book is recommended to all interested in cardiovascular disease and especially hypertension.

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STUDIES IN VISUAL OPTICS. Joseph I. Pascal, B.S., M.A., O.D., M.D., Licentiate in Optometry and in Medicine by the University of the State of New York, Attending Ophthalmologist, New York Polyclinic Medical School and Hospital. Illustrated. The C. V. Mosby Company, St. Louis, 1952. 800 pages, $12.50.

The subject of visual optics is one of the most difficult ones for the student or resident in ophthalmology. The average book dealing with the subject is so full of formulas that the student is soon lost in a maze of mathematical figures. In his book Pascal presents these subjects in a simplified manner that permits the student to understand the underlying principles without delving into higher mathematics.

The book, which is divided into 46 chapters, covers the fields of optics; retinoscopy; refraction, including a discussion of prisms and spectacle lenses, some data on ocular muscles, together with a chapter on contact lenses. The appendix contains a lot of interesting information. The book contains a good index.

Much of the material for this book has appeared in various journals in the fields of ophthalmology and optometry. This has been augmented by a good deal of unpublished material.

The format while good does not come up to the usually good Mosby standard.

The book is especially recommended for the tyro in ophthalmology.

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A SEX GUIDE TO HAPPY MARRIAGE. Edward F. Griffith, Member of the Royal College of Surgeons, Licentiate of the Royal College of Physicians. With an Introduction by Robert Latou Dickinson, M.D. Emerson Books, Inc., 251 West 19th Street, New York 11, 1951. 352 pages. $3.00.

Although the reviewer cannot agree with all the author's personal viewpoints, he feels that this is a good book for the doctor to recommend to his patients. It can be particularly valuable for those individuals who are contemplating marriage or for those who have problems relating to sex. It may also be recommended to the physician himself because of its summarization in simplified form of a varied fund of useful knowledge, including sexual relations, contraceptives, and marriage counseling.